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(54) Title: METHOD FOR THE DIFFERENTIAL DIAGNOSIS OF PARKINSONIAN SYNDROMES

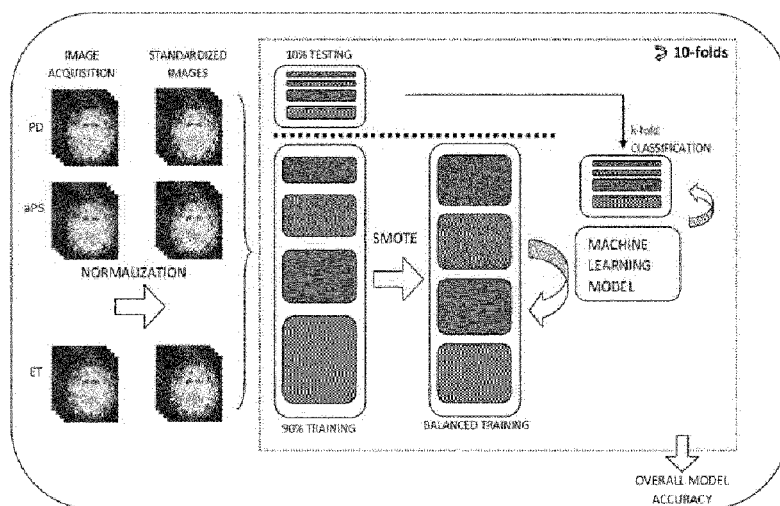


FIG.1

(57) Abstract: The present invention provides computerized analysis methods using machine learning models with nuclear neuroimaging data, preferably the neuroimaging data of [^{123}I]FP-CIT SPECT, to differentiate PS. The inventors have developed a methodology to process this type of scan, and have built models that are able to distinguish the different entities of parkinsonism. The examples of the invention present preliminary results for the multinomial approach (PD vs. PSP vs. MSA vs. CBD vs. VP vs. DIP vs. ET), and also give binary models which are particularly robust and of interest (PD vs. VP and PD vs. PSP). The information provided by the developed computational solution potentially supports clinical decision-making in nuclear medicine.

Method for the differential diagnosis of Parkinsonian syndromes

This invention relates to the field of Parkinsonian syndromes (PS) diagnosis and prognosis, and more precisely to computerized analysis methods for the differential diagnosis and classification of PS into three groups: patients with Parkinson's disease (PD), atypical PS (PS caused by other neurodegenerative diseases, aPS), and secondary parkinsonism. By using the methods of the present invention it is possible to subclassify the patients with atypical PS into other three groups: progressive supranuclear palsy (PSP), multiple system atrophy (MSA), and corticobasal degeneration (CBD); and also, it is possible to subclassify the patients with secondary PS into other two groups: Vascular parkinsonism (VP) and drug-induced parkinsonism (DIP).

BACKGROUND OF THE INVENTION

Parkinsonian syndromes (PS) are among the most common neurodegenerative disorders. PS comprise three etiologically different major entities: Parkinson's disease (PD), atypical PS (PS caused by other neurodegenerative diseases, aPS), and secondary parkinsonism. The group of aPS includes progressive supranuclear palsy (PSP), multiple system atrophy (MSA), corticobasal degeneration (CBD). Vascular parkinsonism (VP) and drug-induced parkinsonism (DIP) belong to the category of secondary parkinsonism. Essential tremor (ET) and other tremor syndromes are further common differential diagnoses additional to PD and aPS.

The main features of neurodegenerative disorders often overlap, and early signs and symptoms can be difficult to diagnose. For example, the classic clinical features of PD that are associated with degeneration of the nigrostriatal pathway (namely tremor, rigidity, and bradykinesia) can also be present in patients with CBD, ET, DIP, or VP, particularly in the early stages of disease. Clinicopathological studies have revealed that ~75% of parkinsonian patients prove to have PD at autopsy, and about 80% of patients misdiagnosed as having PD actually have MSA or PSP. Thus, accurate biomarkers for the differential diagnosis of PS are urgently needed.

Nuclear imaging may help to establish a correct diagnosis. [123I]FP-CIT SPECT allows to evaluate in vivo the state of the presynaptic nerve terminals in the nigrostriatal pathway by imaging the striatal dopamine transporter (DAT). It is highly demanded in routinary clinical practice as a tool for identifying neurodegenerative parkinsonism, and because of its approved license in Europe and United States, its use is widespread. It has demonstrated high accuracy to discard neurodegeneration when the clinical presentation is parkinsonian, such it is the case

of ET [Benamer et al., 2000. *Mov Disord*.15:503-10]. Unfortunately, neither visual read by nuclear-medicine specialists nor striatal DAT semi-quantification with available methods and software accurately differentiate PS. However, such methods may be suboptimal for two main reasons: the specialist's introduction of a certain degree of subjectivity in the visual interpretation and in the manual region-of-interest (ROI) delineation and focusing primarily on DAT uptake in the striatum, thus missing the extent of the radioligand binding in other brain regions. In contrast, voxel-based analysis has proven to be a reliable and unbiased tool for the examination of whole-brain imaging. Statistical Parametric Mapping (SPM) is one of the most popular tools for whole-brain voxel-based analysis and some studies have used it with success in the differentiation of PD from other PS. In particular, previous studies have shown that there are significant differences in DAT imaging between PD and VP, and aPS [Gerschlagier et al., 2002. *Mov Disord*. 17:518-23; Seppi et al., 2006. *Arch Neurol*. 63:1154-1160; Goebel et al., 2011. *Eur J Nucl Med Mol Imaging* 38(4):702-10; Oh et al., 2012. *J Nucl Med* 53(3):399-406].

Computationally efficient techniques to process voxel-based data are increasingly outperforming the classical methods for neuroimaging assessment. In this context, machine learning provides an exceptional framework to work with, providing methodology to handle with high dimensional data and in turn, to exploit all the information contained in the image [Klöppel et al., 2012. *NeuroImage* 61(2), 457–463].

There is a continuing need for efficient methods that allow for differential diagnosis of parkinsonian syndromes.

BRIEF DESCRIPTION OF THE INVENTION

The present invention provides computerized analysis methods using machine learning models with nuclear neuroimaging data, preferably the neuroimaging data of [¹²³I]FP-CIT SPECT, to differentiate PS. The inventors have developed a methodology to process this type of scan, and have built models that are able to distinguish the different entities of parkinsonism. The examples of the invention present preliminary results for the multinomial approach (PD vs. PSP vs. MSA vs. CBD vs. VP vs. DIP vs. ET), and also give binary models which are particularly robust and of interest (PD vs.VP and PD vs. PSP). The information provided by the developed computational solution potentially supports clinical decision-making in nuclear medicine.

By using the methods of the present invention it is possible to forecast the rate of disease progression, to support therapeutic decision-making, non-invasive and time-saving diagnosis, and to monitor potential therapeutic effects.

5 Then, a **first aspect** of the invention relates to a computer implemented method for the differential diagnosis of parkinsonian syndromes, hereinafter first method of the invention, comprising:

- 10 a) administering at least one compound which is suitable for collecting image data, which is capable of crossing the blood brain barrier and which can associate with a Dopamine Transporter (DAT) to a human being,
- b) measuring said compound's distribution within the brain using an image modality at least at a time point X_1 ; and
- c) measuring said compound's association with DAT within the brain at least at a time point X_2 , wherein X_2 is later than X_1 .

15 Medical imaging is a general approach to detect subtle differences in the composition, morphology or other behavior in organs as can be imaged by different techniques and equipment (ie. modalities) and relate these differences to clinical phenomena of interest. Image data can be obtained from various sources including for example T1 weighted Magnetic
20 Resonance Imaging ("T1w MRI"), T2 weighted MRI ("T2w MRI"), Proton Density weighted MRI ("PD MRI"), Photon Emission Tomography ("PET"), Single Photon Emission Computer Tomography ("SPECT") and Computer Tomography ("CT").

Then, in a preferred embodiment of the invention the image data are collected using one or
25 more imaging modalities selected from the group consisting of MRI, including structural, spectroscopic, functional, diffusion, and magnetization transfer MRI, near infrared, optical imaging, microwave imaging, X-ray, ultrasound, PET, SPECT, CT, scintigraphy, tomosynthesis, fluoroscopy, portal imaging, and combinations thereof. In a more preferred embodiment, the imaging modality is SPECT and still more preferably is [^{123}I]FP-CIT SPECT.

30 In another preferred embodiment, the method of the invention also comprises:
d) comparing the obtained results with an appropriate control;
and classified the human of step (a) in the group of humans with Parkinson's disease (PD), progressive supranuclear palsy (PSP), multiple system atrophy (MSA), corticobasal
35 degeneration (CBD); vascular parkinsonism (VP), drug-induced parkinsonism (DIP), or essential tremor (ET).

In a particular embodiment, the method of the invention is capable of the differential diagnosis of Parkinson's disease (PD) versus vascular parkinsonism (VP). In another particular embodiment, the method of the invention is capable of the differential diagnosis of Parkinson's disease (PD) versus progressive supranuclear palsy (PSP).

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In another preferred embodiment, the appropriate control is a computer a statistical image-based predictive model.

More preferably the a computer a statistical image-based predictive model is obtained by incorporating one or more image-derived features derived from at least one image comprising information related to said clinical state, wherein said statistical image-based model is established by providing a correlation function between one or more image features and a future value of a clinical variable that represents a measure on said clinical scale, and establishment of said statistical image-based model is realized by acquiring data from a group of training subjects.

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In another preferred embodiment, the method of the invention also comprises stabilizing and normalizing the obtained images by computer. More preferably the images are spatially normalized into the standard stereotactic MNI (Montreal Neurological Institute) space. Still more preferably, the images are also intensity normalized fitting the non-specific binding voxel values to an α -stable distribution [Salas-Gonzalez et al., 2013].

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In another preferred embodiment, the method of the invention also comprises an intensity normalization which allows harmonizing the non-specific binding of all single scans, which is essential to correct for the inter-individual variability and to generalize the model to other centers with other SPECT devices.

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In another preferred embodiment, the image-derived features are 102 characters corresponding to the 90 regions defined in the automated anatomical labels (AAL) atlas. And to masks for the posterior, anterior and ventral parts of putamen and caudate, are the 12 additional brain regions resulting in 102 brain regions were used to build de predictive models.

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A **second aspect** of the invention relates to a computer implemented method for the differential diagnosis of parkinsonian syndromes, hereinafter second method of the invention, that comprises comparing the image data collected as described in the first method of the invention with a computer statistical image-based predictive model; and classified the human of step (a) in the group of humans with Parkinson's disease (PD), progressive supra-nuclear palsy (PSP),

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multiple system atrophy (MSA), corticobasal degeneration (CBD); vascular parkinsonism (VP), drug-induced parkinsonism (DIP), or essential tremor (ET). It is noted that the method of the second aspect of the invention is not invasive since it is not performed in the human or animal body and executes the differential diagnosis by using the image data collected as described in the first method of the invention.

In a preferred embodiment, the computer a statistical image-based predictive model has been constructed as described in the first method of the invention.

A **third aspect** of the invention relates to a computer implemented method for distinguishing between vascular parkinsonism and Parkinson's disease, hereinafter third method of the invention, comprising the use of the first method of the invention. In a preferred embodiment, the thirdmethod of the invention is implemented in a computer system.

A **fourth aspect** of the invention relates to a computer implemented method for distinguishing between progressive supranuclear palsy and Parkinson's disease, hereinafter fourth method of the invention, comprising the use of the first method of the invention. In a preferred embodiment, the fourthmethod of the invention is implemented in a computer system.

A **fifth aspect** of the invention relates to a computer program stored on a computer usable medium, the computer program comprising software code adapted to perform the steps of any one of the methods of the invention.

A **sixth aspect** of the invention relates to a computer readable storage medium/data carrier comprising the program according to the third aspect of the invention, the computer program performing the steps of any one of the methods of the invention.

The medium in which the computer program is encoded may also comprise transmission signals propagating through space or a transmission media, such as an optical fiber, copper wire, etc. The transmission signal in which the computer program is encoded may further comprise a wireless signal, satellite transmission, radio waves, infrared signals, Bluetooth, etc. The transmission signal in which the computer program is encoded is capable of being transmitted by a transmitting station and received by a receiving station, where the computer program encoded in the transmission signal may be decoded and stored in hardware or a computer readable medium at the receiving and transmitting stations or devices.

Then, a **seventh aspect** of the invention relates to a transmission signal comprising program instructions capable of causing a computer to perform the steps of any one of the methods of the invention.

5 DESCRIPTION OF THE FIGURES

Fig. 1 Diagram with the processing steps for generating the classification models.

Fig. 2 Scatter plot with the 2-dimensional graph of ipsilateral caudate [123I]FP-CIT BPND as function of ipsilateral putamen [123I]FP-CIT BPND.

10 **Fig. 3** Voxel clusters representing significant decreases in [123I]FP-CIT uptake in PD with respect to VP. Areas comprise putamen and caudate nucleus and are represented in MNI normalized MRI scan.

DESCRIPTION OF THE INVENTION

The inventors have surprisingly discovered that SPECT tracers can be used for differentially diagnosing parkinsonian syndromes. Accurate diagnosis will have clinical utility, for example, precise diagnosis is important when counseling patients and families about prognosis and the question of whether a determinate therapy should be undertaken. Our objective is to develop machine learning models with the neuroimaging data of [123I]FP-CIT SPECT to differentiate PS. We herein present methodology to process this type of scan, and built models that are able to distinguish the different entities of parkinsonism. The inventors present preliminary results for the multinomial approach (PD vs. PSP vs. MSA vs. CBD vs. VP vs. DIP vs. ET), and they will also give binary models which are particularly robust and of interest (PD vs. VP and PD vs. PSP).

25 Then, a **first aspect** of the invention relates to a computer implemented method for the differential diagnosis of parkinsonian syndromes, hereinafter method of the invention, comprising:

- a) administering at least one compound which is suitable for collecting image data, which is capable of crossing the blood brain barrier and which can associate with a Dopamine Transporter (DAT) to a human or animal being,
- b) measuring said compound's distribution within the brain using an image modality at least at a time point X_1 ; and
- 30 c) measuring said compound's association with DAT within the brain at least at a time point X_2 , wherein X_2 is later than X_1 .

Preferably the measuring are acquired each 30 seconds, and more preferably over a circular orbit.

Medical imaging is a general approach to detect subtle differences in the composition, morphology or other behavior in organs as can be imaged by different techniques and equipment (ie. modalities) and relate these differences to clinical phenomena of interest. Image data can be obtained from various sources including for example T1 weighted Magnetic Resonance Imaging ("T1w MRI"), T2 weighted MRI ("T2w MRI"), Proton Density weighted MRI ("PD MRI"), Photon Emission Tomography ("PET"), Single Photon Emission Computer Tomography ("SPECT") and Computer Tomography ("CT").

Then, in a preferred embodiment of the invention the image data are collected using one or more imaging modalities selected from the group consisting of MRI, including structural, spectroscopic, functional, diffusion, and magnetization transfer MRI, near infrared, optical imaging, microwave imaging, X-ray, ultrasound, PET, SPECT, CT, scintigraphy, tomosynthesis, fluoroscopy, portal imaging, and combinations thereof. In a more preferred embodiment, the imaging modalitaies are PET or SPECT

It is possible to assess the dopamine transporter *in vivo* with specific ligands, such as [¹²³I]-**2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl)nortropane** (¹²³I-FP-CIT) (*Booij J, Habraken JB, Bergmans P, Tissingh G, Winogrodzka A, Wolters EC, et al. Imaging of dopamine transporters with iodine-123-FP-CIT SPECT in healthy controls and patients with Parkinson's disease. J Nucl Med 1998; 39: 1879– 84*). Other ligands are also possible, for example but not limited to 2beta-carbomethoxy-3beta-(4-iodophenyl)tropane ([¹²³I]beta-CIT (2beta-carbomethoxy-3beta-(4-iodophenyl)tropane) SPECT).

Then, in a more preferred embodiment, the imaging modality is SPECT and still more preferably is [¹²³I]FP-CIT SPECT.

In another preferred embodiment, the method of the invention also comprises:

d) comparing the obtained results with acomputer a statistical image-based predictive model;

and clasiffied the human or animal of step (a) in the group of humans or animals with Parkinson's disease (PD), progressive supranuclear palsy (PSP), multiple system atrophy (MSA), corticobasal degeneration (CBD); vascular parkinsonism (VP), drug-induced parkinsonism (DIP), or essential tremor (ET).

In a particular embodiment, the method of the invention is capable of the differential diagnosis of Parkinson's disease (PD) versus vascular parkinsonism (VP). In another particular embodiment, the method of the invention is capable of the differential diagnosis of Parkinson's disease (PD) versus progressive supranuclear palsy (PSP).

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In another preferred embodiment, the computer a statistical image-based predictive model is addressed via *machine learning* approaches.

Machine learning is a subfield of computer science that evolved from the study of pattern
10 recognition and computational learning theory in artificial intelligence. Machine learning explores the construction and study of algorithms that can learn from and make predictions on data. Such algorithms operate by building a model from example inputs in order to make data-driven predictions or decisions, rather than following strictly static program instructions.

15 *Brain variables definition*

There are two main choices for defining brain variables: the first consists of calculating the mean uptake (i.e. the mean intensity in the image) of anatomically-defined brain regions, namely region-based approach; the second consists of considering all the individual voxels contained in the image as single variables, namely whole-brain voxel-based approach.

20 Variables are calculated using homemade Matlab scripts in conjunction with SPM8 routines.

Variables in the region-based approach are defined as the mean uptake of the 90 regions delineated in the automated anatomical labels (AAL) atlas. Specifically for the differential diagnosis of PS, since a previous study found differences between PD and aPS in the striatal subregions, we additionally created masks for bilateral posterior, anterior and ventral parts of
25 putamen and caudate [Oh *et al.*, 2012. *J Nucl Med* 53(3):399-406]. Thus, a total of 12 striatal subregions were manually drawn by expert nuclear-medicine specialists on a spatially normalized ¹⁸F-DOPA PET template made with 12 normal controls. We used this PET template because it offers higher spatial resolution than SPECT and because the profile of ¹⁸F-DOPA binding is similar to that of [¹²³I]FP-CIT. Finally, the mean uptake of 102 brain regions were used
30 as independent variables to build de predictive models.

Variables in the whole-brain voxel-based approach are defined as the intensity of each single voxel in the brain. In standard MNI space, there are in total 182,545 voxels.

Other variables can be included to build the models giving its possible confounding effect for radioligand uptake, for example but not limited to age, sex, disease duration, severity of the
35 motor symptoms assessed by Hoehn & Yahr scale.

Predictive modelling

The clinical diagnosis is considered the "gold standard" and it is therefore used as dependent variable in the models building. The independent variables are brain variables (region-based or voxel-based) defined above. We will also introduce age and sex as independent variables giving their potential confounding effect in the radioligand uptake.

The models will be built following the pipeline of steps illustrated in the diagram of Figure 1. First, raw data images (scans acquired from the patients) will be processed and normalized according to the steps detailed in the section 'Image processing' above. Second, the data matrix with dependent and independent variables will be defined as in section 'Brain variables definition' above.

Third, a k-fold cross-validation scheme corresponding to an iterative loop of 10-folds will be performed to build the models with the training data and assess the models with the testing data. This scheme randomly splits the data set into $k=10$ parts, 90% is used for training and the remaining 10% for testing, for every $kth=1, 2, \dots, 10$. This strategy prevents over-fitting the model with our dataset thus allowing model generalization for other centers data. As mentioned, for each k-fold iteration the dataset will be splitted in training and testing sets. The training sets will be used for building the model and the testing sets to assess it.

Fourth, since the number of cases in each class (i.e. pathology) is different due to the natural differences in disease prevalence, we will compensate for the side effects of class-imbalance in the training set by combining up-sampling the minority classes and down-sampling the majority classes. This re-sampling strategy may be tackled with, but not limited to, improved modifications of the algorithm SMOTE (synthetic minority oversampling technique) [Chawla *et al.*, 2002. *J Artif Intell Res* 16:341–378]. Different rates of re-sampling, from 0% to 100% by 10%, will be surveyed in order to obtain optimal results. Improved modifications of the SMOTE algorithm may include, random, clusted-based or tomek's distance-based down-sampling and random, or adaptive up-sampling such as ADASYN or BoderlineSMOTE algorithms [Abdi & Hashemi, 2014, To combat multi-class imbalanced problems by means of over-sampling and boosting techniques, *Soft Comput*].

Fifth, once the classes in the training set are balanced, we will perform a feature selection step prior to train the model. This is done to discard non-informative variables. Correlation analyses of the variables will be also conducted in order to prevent from multicollinearity. Feature selection methods may include, but not limited to, wrapper methods such as stepwise regressions and recursive feature elimination algorithm (RFE), or filter methods for quantitative variables such as Student's t-test, Relief-f, or newer methods more reliable in the presence of

class imbalance such as Pearson correlation coefficient, or feature assessment by sliding thresholds (FAST) [Chen & Wasikowski, 2008.ACM, New York 2008; pp 124–132].

Sixth, the model will be trained. Different models of the machine learning family may be used for this purpose. We will survey the most common approaches. In particular, we will focus on algorithms able to extent to the multinomial case, such as support vector machines (one-versus-all approach), linear models such as logistic and multinomial regression with coefficient penalization (e.g. ridge, lasso, elastic), decision trees and rule-based such as random forest, and other methods such as naive bayes, boosting and bagging.

Seventh, for each k-fold, that is, for each k-th trained model, the performance will be assessed on the k-th test set split. Lastly, the final model and performance results were obtained from averaging the ten runs, which were given in area under the receiver operating characteristic (ROC) curve (AUC), sensitivity and specificity in the binary models, and in M-measure/MAUC [Hand and Till, 2001. Mach Learn 45(2):171–186] and extended G-mean [Sun Y, Kamel MS, Wang Y. Boosting for learning multiple classes with imbalanced class distribution. In: Proceeding of the sixth international conference on data mining. ICDM 2006, IEEE, pp 592–602] in the multinomial case.

The predictive model can be obtained by deriving a set of modes of variation of the image features from a plurality of training subjects, selecting a subset of the modes of variation based on a first univariate or multivariate analysis or combination thereof between the modes of variation and at least one clinical variable, and establishing the model based on a second univariate, or multivariate analysis or combination thereof between the selected subset of modes and the at least one clinical variable.

The subjects may be chosen in a number of different ways, understood by a person skilled in the art, in order to discriminate between groups of subjects on the hypothesis that there exists intensity and spatial differences between brain images of individuals in the groups. Groups of subjects need not always include “normal” non-pathological individuals. For example, the classifier may be used to separate between groups of pathological individuals. In order to capture the variability between individual subjects within the statistical models, a large enough number of training subjects must be selected.

For example, pathological individuals of a particular condition (or state of nature) might be classified by the system on the basis of a control group consisting solely of known pathological subjects of that particular condition (in such an embodiment, a different model for the definition of membership within each classification region would be built than one for which the control

group contains known member of each possible condition). In a preferred embodiment, the training subject images and the control subject images are obtained from two distinct groups of subjects in order to ensure statistical independence.

- 5 More preferably a computer-based statistical image-based predictive model is obtained by incorporating one or more image-derived features derived from at least one image comprising information related to said clinical state, wherein said statistical image-based model is established by providing a correlation function between one or more image features and a future value of a clinical variable that represents a measure on said clinical scale, and
10 establishment of said statistical image-based model is realized by acquiring data from a group of training subjects.

The method of the invention also comprises a normalization which allows harmonizing the non-specific binding of all single scans, which is essential to correct for the inter-individual variability
15 and to generalize the model to other centers with other SPECT devices.

Then, in another preferred embodiment, the method of the invention also comprises stabilizing and normalizing the obtained images by computer. More preferably the images are normalized into the standard stereotactic MNI (Montreal Neurological Institute) space. Still more preferably,
20 **the images are also normalized using the non-specific binding voxel values to an α -stable distribution [Salas-Gonzalez *et al.*, 2013. *Neuroimage* 65:449-455].**

Both intensity and spatial characteristics of the image data are calculated and define the features of the images that will be analyzed in later steps. Statistical models are created based
25 on training subject images and define multi-dimensional spaces within which subjects may be represented. These statistical models are merged to create one single, final multi-dimensional classification space or universe. A classifier is built within this classification space based on control group image data and divides the universe of subjects into two or more regions, such that each region defines a space of subjects having a particular condition (or state of nature).
30 This classifier is then used to identify and characterize the disease state of individuals, such as a test patient, based on the location of an individual's representation within the classification space.

In another preferred embodiment, the image-derived features are 102 characters corresponding
35 to the 90 regions defined in the automated anatomical labels (AAL) atlas. And to masks for the posterior, anterior and ventral parts of putamen and caudate, are the 12 additional brain regions resulting in 102 brain regions were used to build de predictive models.

A **second aspect** of the invention relates to a computer implemented method for the differential diagnosis of parkinsonian syndromes, hereinafter second method of the invention, that comprises comparing the image data collected as described in the first method of the invention with a computer a statistical image-based predictive model; and clasified the human of step (a) in the group of humans with Parkinson's disease (PD), progressive supranuclear palsy (PSP), multiple system atrophy (MSA), corticobasal degeneration (CBD); vascular parkinsonism (VP), drug-induced parkinsonism (DIP), or essential tremor (ET).

In a preferred embodiment, the computer a statistical image-based predictive model has been constructed as described in the first method of the invention.

A **third aspect** of the invention relates to a computer implemented method for distinguishing between vascular parkinsonism and Parkinson's disease, hereinafter third method of the invention, comprising the use of the first method of the invention. In a preferred embodiment, the third method of the invention is implemented in a computer system.

A **fourth aspect** of the invention relates to a computer implemented method for distinguishing between progressive supranuclear palsy and Parkinson's disease, hereinafter third method of the invention, comprising the use of the first method of the invention. In a preferred embodiment, the fourth method of the invention is implemented in a computer system.

A **fifth aspect** of the invention relates to a computer program stored on a computer usable medium, the computer program comprising software code adapted to perform the steps of any one of the methods of the invention.

A **sixth aspect** of the invention relates to a computer readable storage medium/data carrier comprising the program according to the third aspect of the invention, the computer program performing the steps of any one of the methods of the invention.

The medium in which the computer program is encoded may also comprise transmission signals propagating through space or a transmission media, such as an optical fiber, copper wire, etc. The transmission signal in which the computer program is encoded may further comprise a wireless signal, satellite transmission, radio waves, infrared signals, Bluetooth, etc. The transmission signal in which the computer program is encoded is capable of being transmitted by a transmitting station and received by a receiving station, where the computer

program encoded in the transmission signal may be decoded and stored in hardware or a computer readable medium at the receiving and transmitting stations or devices.

Then, a **seventh aspect** of the invention relates to a transmission signal comprising program instructions capable of causing a computer to perform the steps of any one of the methods of the invention.

EXAMPLES AND DESCRIPTION OF THE INVENTION

EXAMPLE 1. BINARY DIFFERENTIAL DIAGNOSIS BETWEEN VP and PD

Introduction

Vascular parkinsonism (VP) is a parkinsonian syndrome due to cerebrovascular lesions and characterized by the presence of gait difficulty, symmetrical lower body bradykinesia and postural instability, and the absence of resting tremor. Although recent neuropathology and epidemiological studies have reported hallmarks distinguishing VP from idiopathic Parkinson's disease (PD), overlap in symptoms presentation is not rare and its differentiation is still a clinical challenge, especially at early stages [Zijlmans *et al.*, 2007. *Mov Disord.* 22:1278-85].

The visualization of the dopamine transporter (DAT) through the use of [123I]FP-CIT SPECT is a commonly used tool that may help in the distinction of VP and PD. However, the status of the striatal DAT in VP is controversial due to its heterogeneity and the accuracy in the differential diagnosis is still poor. This heterogeneity has been reflected in a recent study with a large cohort that showed that the [123I]FP-CIT SPECT of about one third of VP cases were normal, while the other two thirds were abnormal, and from which a small percent of cases overlapped the typical imaging pattern of PD [Antonini *et al.*, 2012. *Parkinsonism Relat Disord.* 18:775-80].

The majority of the studies including VP have evaluated [123I]FP-CIT SPECT imaging through visual assessment according to a standardized scale or semi-quantification of striatal ligand uptake (ROI analysis). Such methods may be suboptimal and voxel-based studies including VP series are still lacking.

The objective of this study is to conduct a whole-brain voxel-based comparison between VP and PD using Statistical Parametric Mapping (SPM) and to build predictive models with machine learning algorithms for its differential diagnosis.

Methods

Participants

We included a total of 282 patients with signs of parkinsonism who underwent [123 I]FP-CIT SPECT in the early stages (<5 years from symptom onset) at our centre, from 2002 to 2014. This sample included 202 patients with PD (mean age 64 y) and 80 patients with VP (77 y). A retrospective systematic review of the medical records was performed by neurologists specialist in movement disorders. All patients were diagnosed based on established clinical criteria. Patients were recruited from the Movement Disorders Unit at Hospital Virgen del Rocío (Seville, Spain). All subjects provided informed written consent approved by the local ethics committee.

SPECT imaging

Patients underwent a brain SPECT scan with a dual-head rotating gamma camera (Philips Axis) fitted with LEHR fan-beam collimators. In order to block the thyroid uptake of free radioactive iodide, patients were given potassium perchlorate 500 mg orally 30 min before intravenous injection of 185 MBq of [123 I]FP-CIT (Ioflupane. Datscan®. GE Healthcare). Images acquisition began between 3 and 4 hours after injection of the radioligand. A total of 120 images of 30 seconds each over a 360° circular orbit were acquired on a 128 x 128 matrix (zoom 1.5). Reconstruction was performed by filtered back-projection using a Butterworth filter and further reorientation to obtain transaxial slices.

Image processing

SPECT images were processed with SPM8 (Wellcome Department of Cognitive Neurology, London, UK). The images were first manually reoriented setting the anterior commissure as the coordinate's origin. Each scan was then spatially normalized into the standard stereotactic MNI (Montreal Neurological Institute) space using a homemade [123 I]FP-CIT template and which is publicly available at <http://www.nitrc.org/projects/spmtemplates>, and subsequently smoothed using an isotropic 8 mm full width at half-maximum isotropic Gaussian kernel (FWHM). Next, given that we observed in the histogram of the images a large inter-subject variability due to not only multiplicative but also additive effects (shift in x-axis), we **intensity normalized the images by fitting the non-specific binding voxel values to an α -stable distribution** [Salas-Gonzalez et al., 2013]. This process of normalization allows to harmonize the non-specific binding of all single scans, which is essential to correct for the inter-individual variability and to generalize the model to other centers with other SPECT devices. Asymmetrical SPECTs with more affection on the left side, defined as those with a striatal asymmetry index > 10% ($(\text{right striatum uptake} - \text{left striatum uptake}) / ((\text{right striatum uptake} + \text{left striatum uptake}) / 2)$), were flipped so that the more affected side lied on the right hemisphere.

Brain variables definition

The mean uptake of the 90 regions defined in the automated anatomical labels (AAL) atlas were individuated using a homemade Matlab batch script. Since a previous study found differences between PD and aPS in the striatal subregions [Oh et al., 2012], we additionally created masks for the posterior, anterior and ventral parts of putamen and caudate. Hence, 12 striatal subregions were manually drawn by expert nuclear-medicine specialists on a spatially normalized ^{18}F -DOPA PET template made with 12 normal controls. We used this PET template because it offers higher spatial resolution than SPECT and because the profile of ^{18}F -DOPA binding is similar to that of [^{123}I]FP-CIT. Finally, the mean uptake of 102 brain regions were used to build de predictive models.

10 *Predictive modelling*

The clinical diagnosis was considered the "gold standard" in this study and it was used as dependent variable. The independent variables were the 102 brain regions and age was also introduced as a potential confounder.

To compensate the side effects of class-imbalance, classes were balanced to improve model fitting by combining up-sampling the minority class and down-sampling the majority class through the algorithm SMOTE (synthetic minority oversampling technique) [Chawla et al., 2002. *J Artif Intell Res* 16:341–378]. We used a 50% sampling rate based on the results of a former study of efficiency [Dubey et al., 2014. *Neuroimage* 87:220–241].

Since the number of independent variables was relatively large, regularized algorithms were used. These algorithms weight the independent variables according to its information content, prioritizing some and penalizing others through tunable shrinkage functions. As predictive algorithm, we used the penalized regression models implemented in the R package "glmnet" [Friedman et al., 2011. *The Elements of Statistical Learning - Data Mining, Inference, and Prediction*, Second Edition. Springer Series in Statistics, 2nd ed. 2009, XXII, 745 p. 282 illus]. This algorithm allows to execute both binary logistic and multinomial regressions.

The models were assessed using a 10-fold cross-validation scheme, which randomly splits the dataset into $K=10$ parts, 90% is used for training and the remaining 10% for testing, for every $kth=1, 2, \dots, 10$. This strategy prevents over-fitting the model with our dataset thus allowing model generalization for other centers data. The final model and performance results were obtained from averaging the ten runs, which were given in accuracy for the multinomial case, and in the binary models in area under the receiver operating characteristic (ROC) curve (AUC), sensitivity and specificity. All calculations were done using the R-package "caret" (<http://caret.r-forge.r-project.org/>).

Results

Differential diagnosis PD vs. VP

The SMOTE algorithm up-sampled VP cases and down-sampled PD cases so that a total of 115 samples from each group were used for model fitting. The mean AUC of the 10-fold cross-validation scheme was of $96 \pm 4\%$ (Table 1).

Table 1. Average 10-fold cross-validation performance results (mean $\pm$ standard deviation) for the VP vs. PD glmnet diagnostic predictive model, given in area under the ROC curve (AUC), accuracy, sensitivity (Sens) and specificity (Spec).

Comparison	AUC	Sens	Spec	glmnet parameters
PD vs. VP	0.96 ± 0.04	0.90 ± 0.08	0.90 ± 0.09	$\alpha = 0.1, \lambda = 0.00059$

Discussion

In this study, we have provided accurate methods for distinguishing between VP and PD using [123I]FP-CIT SPECT. We developed predictive models using the quantitative data from the SPECT evaluation of a large cohort of patients.

We have observed in our study what previous studies have been postulating for years: vascular parkinsonism is a different and distinguishable entity from PD; however clinical manifestations and imaging patterns are heterogeneous. Nowadays, [123I]FP-CIT SPECT represents a widely extended and helpful tool to aid the physician in the diagnosis of VP, and numerous studies have worked with its visual assessment and ROI quantification. Some authors reported significant differences in the asymmetry index with respect to PD, but these studies had a small sample size and the sensitivity was as low as 50%. These results have questioned the accuracy of [123I]FP-CIT SPECT for VP diagnosis, and indeed, a very recent study considered the inclusion of cardiac [123I]MIBG SPECT and smell identification UPSIT test for the differential diagnosis [Navarro-Otano *et al.*, 2013. *Parkinsonism Relat Disord.* 20:192-7]. In contrast, other studies have successfully applied elegant methods for distinguishing atypical parkinsonisms and other diseases from PD with DAT SPECT imaging [Scherfler *et al.*, 2005. *Brain* 128:1605-12; Goebel *et al.*, 2011. *Eur J Nucl Med Mol Imaging* 38(4):702-10]

In this study, we have investigated images of VP using these sorts of approaches. We found that in PD, in comparison with VP, the striatal DAT availability is markedly reduced and the AI is significantly higher. SPM analysis revealed significant differences in [123I]FP-CIT uptake in two specular clusters of voxels comprising areas of the striatum. We penalized classification

algorithm and found that glmnet model was able to discriminate VP and PD with 96% of AUC, and a balanced accuracy (sensitivity and specificity) of 90%.

Moreover, results could be improved to 95% accuracy by thresholding the class probability and creating a pool of doubtful cases. For those cases, we assumed the ROI analysis of [123I]FP-CIT SPECT was inconclusive and that it would be necessary to evaluate the clinical profile and the structural neuroimaging to determine a more reliable diagnosis.

This method demonstrated that the use of whole-brain voxel data is a powerful alternative with two great advantages with traditional methods: no a priori assumptions about the location of the ligand uptake and more importantly, the method is conducted in an unbiased and automated fashion.

Finally, it is interesting to argue why these models did not reach 100% accuracy. In our opinion there might be a major limitation influencing the accuracy: our gold standard was based on clinical criteria that was blind to the SPECT, and perhaps a few cases were wrongly diagnosed. Some of the cases that were tagged as VP, even-though they fulfilled the criteria for VP when included in the study, had a PD-like pattern in the scan. It is possible that some of these patients truly had VP with an indistinguishable [123I]FP-CIT SPECT from PD, while others had in reality an underlying PD accompanied with cerebrovascular damage. In that case, updating our models would entail an increase in the accuracy and therefore, a boost in the credibility of the SPECT-aided diagnosis. Nevertheless, to confirm this hypothesis it would be necessary to perform a long term follow-up to verify how these patients evolve clinically, or preferentially, an MRI scan or an anatomopathological examination in the most misleading cases.

In conclusion, this study has provided accuracies above 90% in discriminating between VP and PD via [123I]FP-CIT SPECT. Our study introduces a method for processing voxel-based data: the use of penalized algorithms implemented in R-packages, and provides an automated and therefore objective, fast and efficient solution very beneficial for the nuclear-medicine specialist decision-making.

EXAMPLE 2. BINARY DIFFERENTIAL DIAGNOSIS BETWEEN PSP and PD

Introduction

Progressive supranuclear palsy (PSP) is already recognised as a neurodegenerative parkinsonism with heterogeneous forms. The classical presentation is the Richardson syndrome (PSP-RS) which is clinically characterised by progressive postural instability and falls, gait disturbance, supranuclear vertical gaze abnormalities, and cognitive deficits. Other forms have been recently described, including the PSP with pure akinesia and gait freezing (PSP-PAGF) and the PSP with parkinsonism (PSP-P). The former is characterised by difficulty initiating gait and freezing during walking, writing and speaking, and the latter by asymmetric bradykinesia and rigidity often with a moderate response to levodopa. In the early stages, the clinical picture of PSP in general, and the PSP-P in particular, is often indistinguishable from Parkinson's disease (PD). Whether there are or not distinct biological processes underlying the different phenotypes remains unknown, but there is evidence manifesting a milder pathological tau burden in PSP-P than in PSP-RS [Williams & Lees, 2009. *Lancet Neurol* 8:270-279].

[123I]FP-CIT SPECT allows to evaluate in vivo the state of the presynaptic nerve terminals in the nigrostriatal pathway by imaging the striatal dopamine transporter (DAT). Unfortunately, neither visual read by nuclear-medicine specialists nor striatal DAT semi-quantification with available methods and software accurately differentiate PSP from PD. one group found reduced [123I]β-CIT SPECT uptake in PSP than in PD and elaborated a statistical method to classify them [Seppi *et al.*, 2006. *Arch Neurol*. 63:1154-1160; Goebel *et al.*, 2011. *Eur J Nucl Med Mol Imaging* 38(4):702-10]. Also, a recent study evaluated 19 patients with PSP-RS with [123I]FP-CIT PET and found a striatal subregional biomarker with an accuracy above 90% to distinguish from PD. However, the sample sizes of these series were moderate (less than 20 PSP patients) and to our knowledge, none of the existing studies to date has addressed the differential diagnosis of PD and PSP-P with neuroimaging techniques.

The objective of the present study was to compare the [123I]FP-CIT SPECT between PSP and PD and to create machine learning models for its differential diagnosis. Given that differentiating PSP-P and PD is particularly troublesome, and that the PSP-tau burden in substantia nigra is lower in PSP-P, we further subdivided the PSP group into PSP-P and non-PSP-P subgroups (PSP-RS and PSP-PAGF), and hypothesized that the [123I]FP-CIT SPECT would be differently affected in these groups.

Methods

Participants

We included a total of 272 patients with signs of parkinsonism who underwent [123]FP-CIT SPECT in the early stages (<5 years from symptom onset) at our centre, from 2002 to 2014. This sample included 202 patients with PD (mean age 64 y) and 70 patients with PSP (72 y). A retrospective systematic review of the medical records was performed by neurologists specialist in movement disorders. All patients were diagnosed based on established clinical criteria. PSP patients were divided into three subtypes (PSP-RS, PSP-P and PSP-PAGF) based on previously defined clinical criteria [Williams et al., 2005. *Brain* 128:1247–1258]. Patients were recruited from the Movement Disorders Unit at Hospital Virgen del Rocío (Seville, Spain). All subjects provided informed written consent approved by the local ethics committee.

SPECT imaging, Image processing, Brain variables definition, Predictive modelling sections are described above in Example 1.

Results

Differential diagnosis PD vs. PSP

The SMOTE algorithm up-sampled PSP cases and down-sampled PD cases so that a total of 115 samples from each group were used for model fitting. The mean AUC of the 10-fold cross-validation scheme was of $89 \pm 7\%$ (Table 1).

Table 1. Average 10-fold cross-validation performance results (mean $\pm$ standard deviation) for the PSP vs. PD glmnet diagnostic predictive model, given in area under the ROC curve (AUC), accuracy, sensitivity (Sens) and specificity (Spec).

Comparison	AUC	Sens	Spec	glmnet parameters
PD vs. PSP	0.89 ± 0.07	0.82 ± 0.12	0.83 ± 0.11	$\alpha = 0.1, \lambda = 0.0052$
PD vs. PSP (PSP-P excluded)	0.95 ± 0.07	0.90 ± 0.11	0.89 ± 0.11	$\alpha = 0.1, \lambda = 0.00055$

Discussion

In this study, we have provided accurate methods for distinguishing between PSP and PD using [123]FP-CIT SPECT. We developed predictive models using the quantitative data from the SPECT evaluation of a large cohort of patients.

The results of our study are in line with the clinicopathological studies that found a distinct severity of disease between the subtypes of PSP. In particular, we have observed that the affection of the nigrostriatal pathway seen by DAT imaging is similar between PSP-P and PD,

and that the other subtypes of PSP, namely the classical PSP-RS and PSP-PAGF, are more affected than the two former. This difference has allowed us to distinguish PD vs. non-PSP-P (PSP-RS and PSP-PAGF) with 95% AUC, and a balanced accuracy (sensitivity and specificity) of ~90%.

- 5 This was observed because a high percent of missclassifications (10/13) in the first model (PD vs all PSP) corresponded to the subgroup of patients with the parkinsonian PSP subtype (PSP-P). Patients with this subtype of PSP display a similar phenotype of PD, very often clinically indistinguishable, and in fact, the pathological burden is less severe than in other subtypes of PSP [Williams et al., 2007. *Brain* 130:1566–1576]. For this reason, we conclude that PSP-P and
 10 PD are indistinguishable with [123 I]FP-CIT SPECT.

EXAMPLE 3. MULTINOMIAL DIFFERENTIAL DIAGNOSIS AMONG PARKINSONISMS

Methods

Participants

- 15 We included a total of 572 patients with signs of parkinsonism who underwent [123 I]FP-CIT SPECT in the early stages (<5 years from symptom onset) at our centre, from 2002 to 2014. This sample included 202 patients with PD (mean age 64 y), 70 with PSP (72 y), 13 with MSA (66 y), 24 with CBD (72 y), 80 with VP (77 y), 47 with DIP (70 y) and 133 with ET (69 y). A retrospective systematic review of the medical records was performed by neurologists specialist
 20 in movement disorders. All patients were diagnosed based on established clinical criteria. Patients were recruited from the Movement Disorders Unit at Hospital Virgen del Rocío (Seville, Spain). All subjects provided informed written consent approved by the local ethics committee.

SPECT imaging, Image processing, Brain variables definition, Predictive modelling sections are described above in Example 1.

25 Results

Multinomial differential diagnosis

The results for the multi-class approach are still preliminar. We have achieved a global accuracy of 79%. In this analysis, all aPS cases (PSP, MSA and CBD) were merged into a single group.

	Prediction
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	PD	aPS	VP	ET	DIP
PD	187	21	11	1	5
aPS	6	65	6	1	5
VP	4	3	43	6	7
ET	5	5	15	125	12
DIP	0	0	2	0	18

Discussion

In this study, we have provided methods for discriminating several types of parkinsonian syndromes using [123I]FP-CIT SPECT. We developed predictive models using the quantitative data from the SPECT evaluation of a large cohort of patients and our results are still moderate.

However, these results for the multi-class approach are still preliminar. We have achieved a global accuracy of 79%. In this analysis, all aPS cases (PSP, MSA and CBD) were merged into a single group. As expected and commented in Example 2, PSP-P patients were wrongly classified into the PD group, thus decreasing the sensitivity to diagnose aPS. Regarding VP, there were 11 cases misdiagnosed as PD, which is not very surprising since, lacking autopsy, it is possible that some cases fulfilling clinical criteria for VP had in reality PD with cerebrovascular damage. There were also 15 cases misdiagnosed as ET, which is in line with previous studies that found ~20% of VP cases with normal DAT scan [Antonini et al., 2012]. Lastly, there is no evidence that DIP is a different entity in DAT SPECT, and for this reason, further research will be performed to clarify why this group showed this low classification accuracy.

CLAIMS

1.- A computer implemented method for the differential diagnosis of parkinsonian syndromes, hereinafter method of the invention, comprising:

- 5 a) administering at least one compound which is suitable for collecting image data, which is capable of crossing the blood brain barrier and which can associate with a Dopamine Transporter (DAT) to a human or animal being,
- b) measuring said compound's distribution within the brain using an image modality at least at a time point X_1 ; and
- 10 c) measuring said compound's association with DAT within the brain at least at a time point X_2 , wherein X_2 is later than X_1 .

2.- A computer implemented method for the differential diagnosis of parkinsonian syndromes, that comprises comparing the image data collected as described in the first method of the invention with a computer a statistical image-based predictive model; and clasified the human of step (a) in the group of humans with Parkinson's disease (PD), progressive supranuclear palsy (PSP), multiple system atrophy (MSA), corticobasal degeneration (CBD); vascular parkinsonism (VP), drug-induced parkinsonism (DIP), or essential tremor (ET).

15

20 3.- The computer implemented method according to any one of claims 1-2, wherein the image data are collected using one or more imaging modalities selected from the group consisting of MRI, including structural, spectroscopic, functional, diffusion, and magnetization transfer MRI, near infrared, optical imaging, microwave imaging, X-ray, ultrasound, PET, SPECT, CT, scintigraphy, tomosynthesis, fluoroscopy, portal imaging, and combinations thereof.

25 4.- The computer implemented method according to any one of claims 1-3, wherein the image data are collected using SPECT.

5.- The computer implemented method according to any one of claims 1-4, wherein the image data are collected using [^{123}I]FP-CIT SPECT.

30 6.- The computer implemented method according to any one of claims 1-5, wherein the method of the invention also comprises:

 d) comparing the obtained results with an appropriate control;
and clasified the human or animal of step (a) in the group of humans or animals with Parkinson's disease (PD), progressive supranuclear palsy (PSP), multiple system atrophy

(MSA), corticobasal syndrome (CBD); vascular parkinsonism (VP), drug-induced parkinsonism (DIP), or essential tremor (ET).

7.- The computer implemented method according to any one of claims 1-7, wherein the method of the invention also comprises:

d) comparing the obtained results with an appropriate control; and classified the human or animal of step (a) in the group of humans or animals with Parkinson's disease (PD) or vascular parkinsonism (VP).

8.- The computer implemented method according to any one of claims 1-7, wherein the method of the invention also comprises:

d) comparing the obtained results with an appropriate control; and classified the human or animal of step (a) in the group of humans or animals with Parkinson's disease (PD) or progressive supranuclear palsy (PSP).

9.- The computer implemented method according to any one of claims 1-8, wherein the appropriate control is a computer a statistical image-based predictive model.

10.- The computer implemented method according to claim 9, wherein the computer a statistical image-based predictive model is obtained by incorporating one or more image-derived features derived from at least one image comprising information related to said clinical state, wherein said statistical image-based model is established by providing a correlation function between one or more image features and a future value of a clinical variable that represents a measure on said clinical scale, and establishment of said statistical image-based model is realized by acquiring data from a group of training subjects.

11.- The computer implemented method according to any one of claims 1-10, also comprising normalizing by computer the obtained images into the standard stereotactic MNI (Montreal Neurological Institute) space.

12.- The computer implemented method according to any one of claims 1-11, wherein the image-derived features are 102 characters corresponding to the 90 regions defined in the automated anatomical labels (AAL) atlas plus 12 additional brain regions corresponding to the posterior, anterior and ventral parts of putamen and caudate.

13.- A computer program stored on a computer usable medium, the computer program comprising software code adapted to perform the steps of the method according to any one of claims 1-12.

- 5 14.- A computer readable storage medium/data carrier comprising the program according to the third aspect of the invention, the computer program performing the steps of any one of the methods according to any one of claims 1-12.

- 10 15.- A transmission signal comprising program instructions capable of causing a computer to perform the steps of any one of the methods according to any one of claims 1-12.

FIGURES

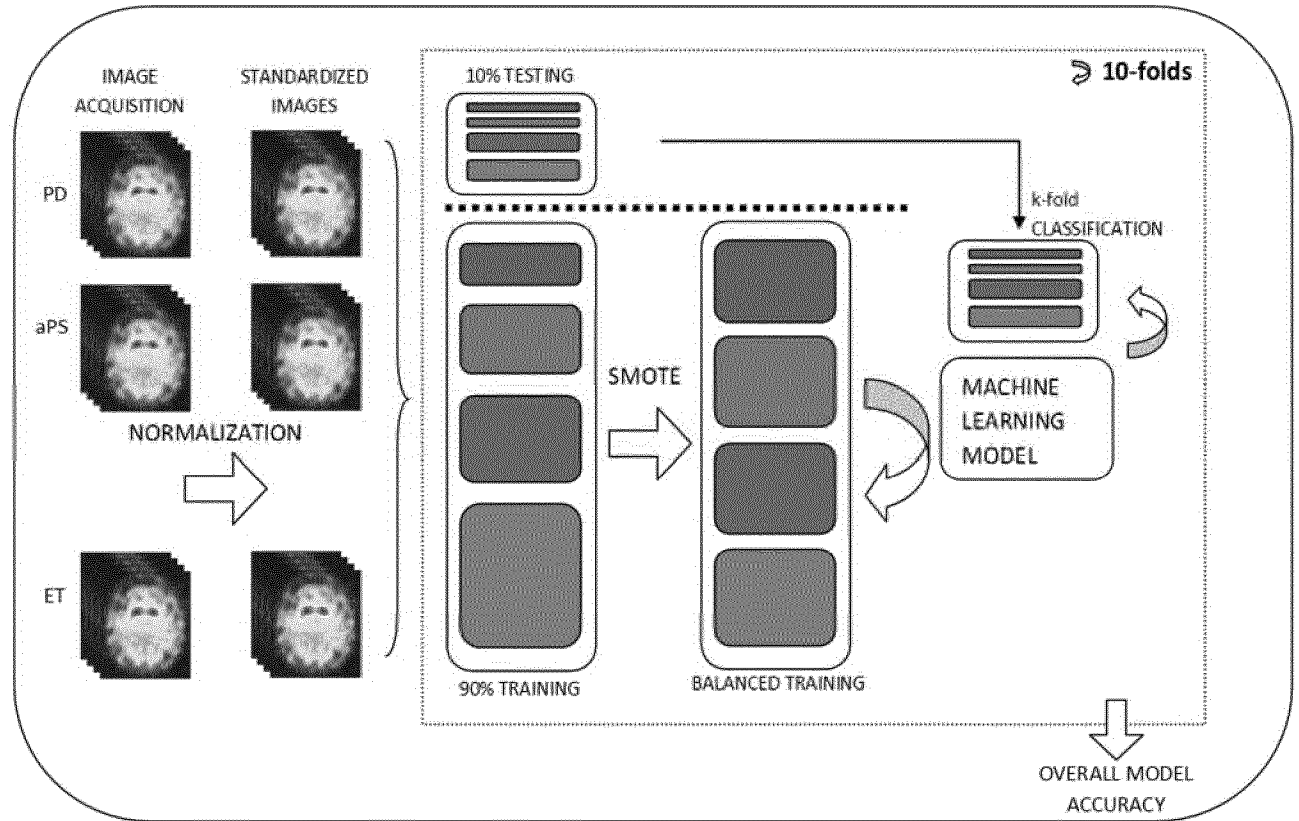


FIG.1

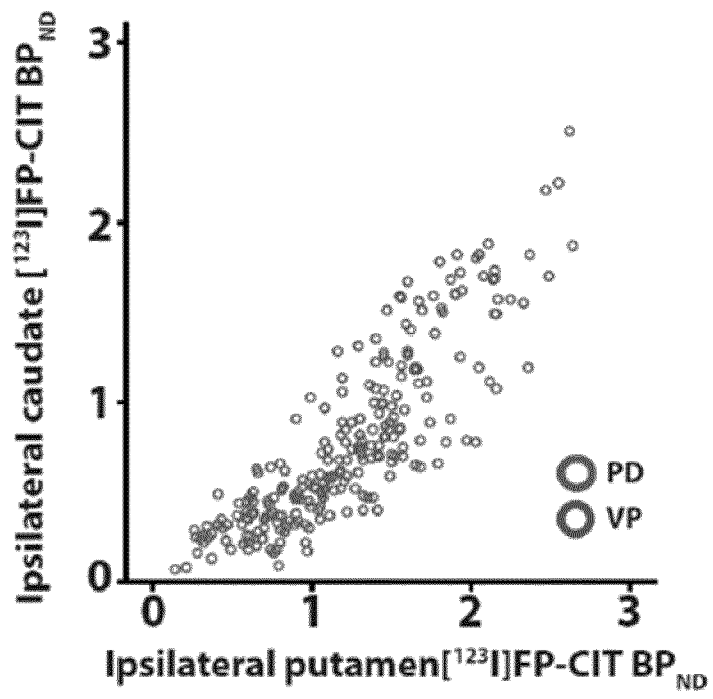


FIG.2

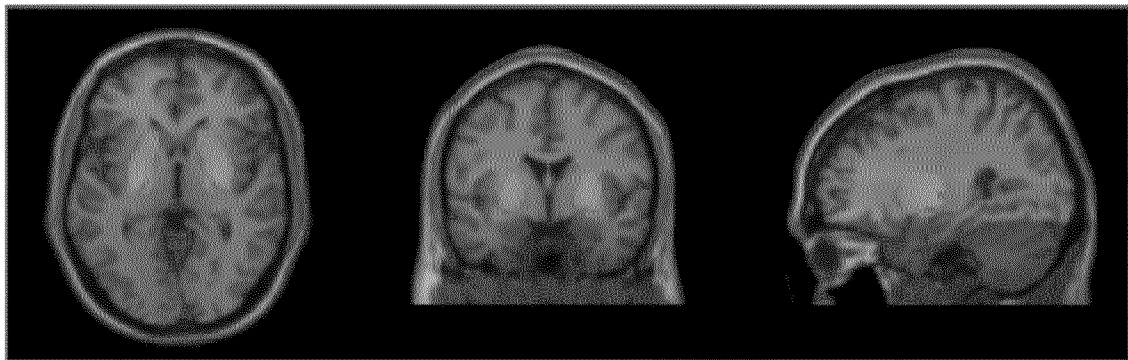


FIG.3

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/067748

A. CLASSIFICATION OF SUBJECT MATTER
INV. G06F19/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
G06F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2013/279771 A1 (WANG JIUN-JIE [TW] ET AL) 24 October 2013 (2013-10-24) paragraph [0007] - paragraph [0022] paragraph [0027] - paragraph [0037] paragraph [0042] figures 1,8 -----	1-15



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

28 October 2015

Date of mailing of the international search report

04/11/2015

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2015/067748

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2013279771	A1	24-10-2013	NONE
