Classification of Alzheimer's disease and Parkinson's disease using a support vector machine and probabilistic outputs

Asuka Hatabu¹, Masafumi Harada², Yoshitake Takahashi³, Shunsuke Watanabe¹
Kenya Sakamoto¹, Kousuke Okamoto⁴, Norihito Kawashita⁵, Yu-Shi Tian¹, Tatsuya Takagi^{1*}

¹Graduate School of Pharmaceutical Science, Osaka University, 1-6 Yamadaoka, Suita, Osaka, 565-0871, Japan

²Graduate School of Biomedical Sciences, the University of Tokushima,
2-24, Shinkura-cho, Tokushima, 770-8501, Japan

³FUJIFILM RI Pharma Co., Ltd., 2-14-1, Kyobashi, Chuo-ku, Tokyo, 104-0031, Japan

⁴Faculty of Pharmaceutical Science, Hokuriku University, Kanagawa-cho. Ho 3, Kanazawa, Ishikawa, 920-1181, Japan

⁵Graduate School of Science and Engineering Faculty of Science and Engineering, Kindai University,
3-4-1 Kowakae, Higashiosaka City, Osaka 577-8502, Japan

*E-mail: ttakagi@phs.osaka-u.ac.jp

(Received October 3; accepted November 27; published online December 12)

Abstract

Alzheimer's disease (AD) and Parkinson's disease (PD) are both prominent central nervous system diseases that are frequently diagnosed and studied using brain single-photon emission computed tomography (SPECT). Owing to divergent clinical features, AD and PD are often considered distinct diseases; however, it is difficult to distinguish AD from PD on SPECT. Tools for objectively analyzing differences between AD and PD on SPECT images are not currently available. To construct a model for discriminating AD from PD in Japanese patients, we used a support vector machine (SVM) and SPECT images acquired at two different time points after radiotracer injection to extract the determinant regions for classification. We assessed SPECT images from 68 Japanese patients with AD or PD. After pre-processing noise voxels, a non-linear SVM classification with Gaussian kernels was adopted to construct the predictive model. The best SVM model was highly accurate for distinguishing AD from PD. The accuracy of this model was 98.1% for leave-one-out cross-validation and 78.6% for the test set. Our data showed that the temporal, sub-lobar, parietal, limbic, and frontal areas exhibited decreased regional cerebral blood flow in AD; whereas the frontal, anterior, parietal, and occipital areas exhibited decreased regional cerebral blood flow in PD. Here, we present a useful SVM model for classifying AD versus PD using SPECT images and show the utility of two-time-point SPECT imaging for AD/PD discrimination.

Key Words: Alzheimer's disease, Parkinson's disease, single photon emission computed tomography, support vector machine, regional cerebral blood flow, computer-aided diagnosis

Area of Interest: Emerging new technology

1. Introduction

Alzheimer's disease (AD) and Parkinson's disease (PD) are two major central nervous system diseases that are particularly prevalent in aging populations. According to the *World Alzheimer Report 2016*, the number of patients with dementia worldwide was estimated to be 47 million in 2016 and is projected to reach 131 million by 2050 [1]. Among individuals with dementia, 60–70% are thought to have AD [2]. Similarly, PD is a common neurodegenerative disorder that affects 6.5 million people and is the cause for approximately 117,400 global annual deaths [3]. Good clinical practices, including early diagnosis and appropriate treatment are increasingly important in age-related diseases such as AD and PD. Single-photon emission computed tomography (SPECT) is a frequently used method for the clinical diagnosis of neurodegenerative disease. SPECT visualizes regional cerebral blood flow (rCBF) by imaging a radiopharmaceutical tracer using a camera that rotates around the head of the patient. Diagnostic decisions are then made by physicians in accordance with SPECT findings. According to a multicenter study [4], the diagnostic accuracy of dementia is better when physicians use SPECT rather than MRI; this is especially so for experienced clinicians who can reliably evaluate this type of imaging. However, SPECT has the problem that the diagnostic accuracy depends upon the physician's experience.

Numerous studies have reported methods for distinguishing patients with AD from healthy cases [5-8], but few studies have described methods for distinguishing patients with AD from other types of dementia [9]. To our knowledge, no study to date has described the classification of AD versus PD using SPECT imaging. The primary reason for this gap in the literature is presumed to be that these diseases have separate clinical features; PD has been traditionally classified as a motor disorder, whereas AD was considered to primarily affect cognitive domains. On the contrary, it is becoming clear that many patients with PD also exhibit dementia as a complication [10]. Additionally, studies have reported significant similarities between patients with AD and those with PD with dementia [11] or depression [12] on SPECT imaging. Indeed, some patients with PD exhibit histological lesions that are similar to those typically seen in AD [13, 14]. Thus, a method to distinguish patients with AD from those with PD is required, using advanced imaging modalities such as SPECT.

N-isopropyl-p-iodoamphetamine (^{123}I -IMP) is a radioactive tracer used for CBF SPECT that has an initial distribution that is proportional to rCBF. Hence, SPECT imaging is typically performed 15–30 min after ^{123}I -IMP administration. Several hours after injection, it is known that ^{123}I -IMP shows an accumulation pattern that varies from its initial distribution owing to the redistribution phenomenon. However, the usefulness of such an accumulation pattern is not known.

A support vector machine (SVM) is a powerful tool for solving classification problems by standardizing margin maximization. Thus, SVM is frequently used for the classification of brain images [15, 16]. Although machine learning methods generally require large-scale training data, SVM has been used for small data sets of brain images. Moreover, Platt [17] devised a method that converts SVM outputs from a classification into a probability. For cases of dementia associated with PD, the probability evaluation can be more appropriate than a binary classification and can also be useful for the diagnosis.

In this study, we constructed a SVM model with good predictive ability for classifying SPECT images of Japanese patients with AD and PD. Unlike in other studies, we performed SPECT at two different time points after ^{123}I -IMP injection (30 min and 180 min) in each patient. This is the first report to describe the utility of two-time-point SPECT and important regions for AD/PD discrimination on SPECT images.

2. Material and Methods

2.1 Subject and data preprocessing

We enrolled patients who needed SPECT imaging for diagnosis at the Tokushima University Hospital between April 2005 and March 2010. Radiologist at Tokushima University Hospital made diagnostic decisions with other experts (neurologists, psychiatrists, neurosurgeons). Only subjects who were diagnosed with AD or PD were included in this study. The study was conducted in accordance with the Declaration of Helsinki and all data used in the study were collected with the approval of the Ethics Committee of Tokushima University and Research Ethics Committee (Number: 277), Graduate School of Pharmaceutical Sciences, Osaka University (Number: 28-1). All subjects provided written informed consent prior to study inclusion.

The study included a total of 68 patients: 24 patients with AD and 44 patients with PD. For SPECT, we used a two-detector apparatus (E.CAM dual-head gamma camera, Toshiba Medical Systems Corp., Tokyo, Japan) with fan beam collimators and injected ^{123}I -IMP as a radioisotope tracer for cerebral perfusion. SPECT images were acquired in a 64×64 matrix by continuous rotation for 28 min (7 rotations, 4 min/rotation) after the injection of ^{123}I -IMP (111 MBq). Images were reconstructed using the ordered-subset expectation maximization method algorithm. The μ -map obtained from the projection data was used for both attenuation correction and scatter correction when transmission-dependent convolution subtraction was applied. Images were acquired at two time points 30 and 180 min after ^{123}I -IMP injection (hereinafter referred to as “early images” and “delayed images,” respectively). Early images were typically used for clinical diagnosis, while delayed images were used for our analysis in order to account for the possibility of differences in the brain distribution of radioligand over time according to the characteristics and extent of disease progression. Thus, we only included patients with both early and delayed image datasets.

Image data were processed as follows. The origin was the center of gravity of the brain. X-axis images were taken left (−78 mm) to right (78 mm), Y-axis images were taken posterior (−112 mm) to anterior (76 mm), and Z-axis images were taken inferior (−50 mm) to superior (84 mm). Each voxel represented a cuboid brain volume of 8 mm^3 ($2 \text{ mm} \times 2 \text{ mm} \times 2 \text{ mm}$). Data were standardized (for an average of 0 and a variance of 1) for each case as shown in **equation (1)**.

$$z_i = \frac{x_i - \bar{x}}{\sigma} \quad (1)$$

where x_i is each voxel in a SPECT image, $\bar{x}$ is the mean of x_i , and σ is the standard deviation calculated using **equation (2)**.

$$\sigma = \sqrt{\frac{\sum_{i=1}^v (x_i - \bar{x})^2}{v}} \quad (2)$$

where v is number of voxels (170,198) contained in a given image.

Further, we applied one-sided t -tests to our data and extracted voxels with p -values < 0.01 . Therefore, clusters consisting of less than 200 voxels were excluded from the data set in order to remove noise. After extraction, each voxel was labeled with a lobe level using the Talairach atlas [18, 19] based on its three-dimensional coordinates. A total of 25 labels were used in the following

analyses.

To construct the model, image data from all 68 patients were randomly split into training data and test data as shown in Table 1. Voxels used for model construction and evaluation are listed with their region labels in Table 2.

Table 1. Numbers of included subjects

Abbreviations: AD, Alzheimer's disease; PD, Parkinson's disease.

Disease	Number of subjects	
	Training set	Test set
AD	19	5
PD	35	9
Total	54	14

Table 2. Talairach atlas labels and numbers of voxels

Abbreviations: AD, Alzheimer's disease; PD, Parkinson's disease; L, Left; R, Right; rCBF, regional cerebral blood flow.

Early image		Delayed image	
rCBF _{AD} > rCBF _{PD}		rCBF _{AD} > rCBF _{PD}	
Talairach label	number of voxels	Talairach label	number of voxels
		Anterior Lobe (L)	154
Frontal Lobe (L)	262	Frontal Lobe (L)	928
Frontal Lobe (R)	2052	Frontal Lobe (R)	995
Occipital Lobe (L)	3782	Occipital Lobe (L)	296
Occipital Lobe (R)	2951		
Parietal Lobe (R)	314		
Posterior Lobe (L)	780		
Posterior Lobe (R)	89		
rCBF _{PD} > rCBF _{AD}		rCBF _{PD} > rCBF _{AD}	
Talairach label	number of voxels	Talairach label	number of voxels
Frontal Lobe (L)	208	Frontal Lobe (L)	220
Limbic Lobe (L)	1795	Limbic Lobe (L)	633
Limbic Lobe (R)	750	Limbic Lobe (R)	230
Parietal Lobe (L)	2491		
Parietal Lobe (R)	750		
Sub-lobar (L)	267		
Sub-lobar (R)	26		
Temporal Lobe (L)	6002	Temporal Lobe (L)	984
Temporal Lobe (R)	1745	Temporal Lobe (R)	236
Total	24264	Total	4676

2.2 SVM

SVM was used for constructing the disease classification model. A flowchart is shown in Figure 1. SVM is a classification scheme devised by Vapnik and Lerner [20] that has been applied in various areas of diagnostic imaging. In this study, we adopted the SVM output to a probability method devised by Platt [17]. We used the `ksvm` function in the Kernlab package (version 0.9-19) of R version 3.1.1 software (<http://www.r-project.org/>). SV type was set to C-svc. Cost C was used as the parameter determining the severity of misclassifications. Adjustment of the parameters is described in the “Parameters” section.

Figure 1. Overview of proposed classification method

Abbreviations: MNI, Montreal Neurological Institute; SPM, Statistical Parametric Mapping; SVM, support vector machine.

2.3 Step-up procedure method

To avoid overfitting, a selection of voxels was performed using a step-up procedure-like method. Owing to the excessive number of voxels (28,940 voxels in total), a normal step-up procedure method would have been too time-consuming and therefore not suitable for our study. Instead, we applied a step-up procedure method for groups; groups were defined in accordance with brain regions. Each group contained multiple voxels (range, 26–6,002). The detailed procedure is described below and an overview is provided in Figure 2.

region	region 1	region 2	region 3	region 4			
voxel	voxel 1	voxel 2	voxel 3	voxel 4	voxel 5	voxel 6	voxel 7
case A	X _{1a}	X _{2a}	X _{3a}	X _{4a}	X _{5a}	X _{6a}	X _{7a}
case B	X _{1b}	X _{2b}	X _{3b}	X _{4b}	X _{5b}	X _{6b}	X _{7b}
case C	X _{1c}	X _{2c}	X _{3c}	X _{4c}	X _{5c}	X _{6c}	X _{7c}

Figure 2. Voxels selection by the step-up procedure method

Step 0. Select one region from 25 voxel groups (regions) as an initial set of voxels. (e.g., Region 1 in Figure 2).

Step 1. Randomly add one remaining region to the initial set and perform SVM classification on the new set. **Step 1** is iterated until all of the regions are added. As a result, 24 SVM models and their evaluations are obtained. After evaluating the models by leave-one-out cross-validation (LOO-CV), the best model is chosen and named “Best model of Step 1.”

Step 2. Two regions used in “Best model of Step 1” are again regarded as initial regions; one more remaining region is added and **Step 1** is repeated. As a result, 23 SVM models are obtained and evaluated. A new best model is chosen and named “Best model of Step 2.” Further, the two best models are compared (“Best model of Step 1” and “Best model of Step 2”). One model is selected as the best model. The regions used in the best model are again regarded as new initial regions and **Step 2** is repeated. The iteration is stopped when no additional regions can be added.

Step 3. **Step 0** to **Step 2** are iterated for all 25 regions. We applied all 25 regions as selected regions in Step 0. Thus, our method included all combinations of region pairs.

In **Step 1** and **Step 2**, the best model was evaluated using predictive accuracy in the training set as a criterion. When two or more models showed the same predictive accuracy, $\ln AD$ was calculated by **equation (3)**. The highest $\ln AD$ was used to identify the best model.

$$\ln AD = \frac{1}{n_{AD}} \sum \log(\text{probability of AD}) \quad (3)$$

where n_{AD} is the number of AD cases.

2.4 Parameters

The following Gaussian kernel function (**equation (4)**) was used to obtain each SVM model. The probability of belonging to a class was calculated from a sigmoid function derived from three-fold cross validation in the ksvm function. Parameter σ in **equation (4)** and parameter C (cost of constraints violation in **equation (5)**) were optimized in the following procedures. The SVM classifier was repeated ten times for each parameter set.

$$k(\mathbf{x}, \mathbf{y}) = \exp(-\sigma \|\mathbf{x} - \mathbf{y}\|^2) \quad (4)$$

$$E(\mathbf{w}) = \|\mathbf{w}\|^2 + c \sum_{i=1}^n L_i(\mathbf{w}) \quad (5)$$

$$L_i(\mathbf{w}) = \sup_{y \in Y} \Delta(y_i, y) + \left\{ \langle \mathbf{w}, \xi(x_i, y) \rangle - \langle \mathbf{w}, \xi(x_i, y_i) \rangle \right\}$$

- 1) Calculate the LOO-CV accuracies of SVM models with all pairs of (C_i, σ_j) where $C_i = 10^i$, ($i = -3, -2, -1, 0$) and $\sigma_j = 10^j$, ($j = -9, -8, \dots, -1$), and then select the SVM model with the best LOO-CV accuracy. Set (C_i, σ_j) , used in the model is marked as $(C_{\max}, s)$.
- 2) Calculate the LOO-CV accuracies of SVM models with all pairs of $(C_{\max}, \sigma)$ where $\sigma = s/10, 3s/10, 5s/10, 7s/10, 9s/10, s, 2s, 4s, 6s, 8s, 10s$ and then select the SVM model with the best LOO-CV accuracy.

A threshold of probability of PD obtained from the SVM model was set to 0.5, which meant that when the probability of PD was calculated to be larger than 0.5, the judgement was PD; otherwise the judgement was AD.

3. Results

3.1 Predictive accuracy of the SVM model

When the frontal lobe (delayed image, left hemisphere, $\text{rCBF}_{AD} > \text{rCBF}_{PD}$) was used as the initial region, a model with the highest accuracy for the training set was achieved. We obtained the optimized parameters values of $\sigma = 9 \times 10^{-5}$ and $C = 1$. The accuracy rates were 98.1% for the LOO-CV and 78.6% for the external test (Table 3). Sensitivity (accuracy for predicting AD) and specificity (accuracy for predicting PD) for the LOO-CV were 94.7% and 100%, respectively. Sensitivity and specificity for the test set were 40.0% and 100%, respectively. Figure 3 shows the evaluations of probability for each patient in the best model from this study. For the training set, only one case of AD was misclassified as PD with a probability of nearly 100%. For the test set, three AD misclassifications occurred.

Table 3. SVM classification performance

The frontal lobe region (delayed image, left hemisphere, $rCBF_{AD} > rCBF_{PD}$) was used as the initial region. Both early and delayed images were used in the data set. Optimized parameters: $\sigma = 9 \times 10^{-5}$, $C = 1$.

Abbreviations: AD, Alzheimer's disease; PD, Parkinson's disease; rCBF, regional cerebral blood flow; SVM, support vector machine.

Accuracy (%)	AD	PD	Total
Training set	18/19 (94.7)	35/35 (100)	53/54 (98.1)
Test set	2/5 (40.0)	9/9 (100)	11/14 (78.6)

Figure 3. Evaluations of probability

(A) Training set and (B) test set. Error bars represent the standard deviations of probabilities belonging to the PD class, and were calculated from SVM models that were built repeatedly 10 times. Abbreviations: AD, Alzheimer's disease; PD, Parkinson's disease; SVM, support vector machine.

3.2 Step-up procedure improved predictive accuracy

We used the LOO-CV accuracy value to evaluate improvements in the SVM model during the step-up procedure method. When total accuracy values calculated from several models were the same, we selected the model with the highest *lnAD* in **equation (3)**. Figure 4 shows changes in total accuracy during the step-up procedure method. In some steps where total accuracy of the training set did not increase, *lnAD* was improved. Total accuracy values for the test set increased until step 6 and subsequently decreased.

Figure 4. Changes in total accuracy rate during the step-up procedure method

3.3 Important regions for the classification

The model with the highest accuracy consisted of 13 regions (Table 4) including 5,288 voxels. The temporal, sub-lobar, parietal, limbic, and frontal areas exhibited decreased rCBF in patients with AD, whereas the frontal, anterior, parietal, and occipital areas exhibited decreased rCBF in patients with PD. Six regions were selected from early images and seven regions were selected from delayed images.

Table 4. Selected regions and numbers of voxels

Abbreviations: AD, Alzheimer's disease; PD, Parkinson's disease.

Step	Selected region			Number of voxels	Total voxels
	Cluster localization	Early / Delayed	Blood flow rate		
-	Frontal Lobe (Left)	Delayed	AD > PD	928	-
1	Anterior Lobe (Left)	Delayed	AD > PD	154	1082
2	Temporal Lobe (Right)	Delayed	PD > AD	236	1318
3	Sub-lobar (Left)	Early	PD > AD	267	1585
4	Sub-lobar (Right)	Early	PD > AD	26	1611
5	Temporal Lobe (Left)	Delayed	PD > AD	984	2595
6	Parietal Lobe (Right)	Early	PD > AD	750	3345
7	Limbic Lobe (Left)	Delayed	PD > AD	633	3978
8	Frontal Lobe (Left)	Early	PD > AD	208	4186
9	Parietal Lobe (Right)	Early	AD > PD	314	4500
10	Limbic Lobe (Right)	Delayed	PD > AD	230	4730
11	Frontal Lobe (Left)	Early	AD > PD	262	4992
12	Occipital Lobe (Left)	Delayed	AD > PD	296	5288

4. Discussion

4.1 A good model for AD versus PD classification

Our SVM model achieved accuracy ratios of 98.1% and 78.6% in the training and test sets, respectively, indicating good utility for classifying cases of AD and PD. The predictive accuracy of our model is comparable to that in similar previous reports: SVM used to classify patients according to disease state (vascular Parkinsonism or PD) produced an accuracy of 90.4% [21], whereas SVM used to distinguish patients with AD and those with mild cognitive impairment (MCI) from healthy control subjects had accuracy values of 94.1% and 88.9%, respectively [22]. SVM used to classify patients with AD from healthy control subjects had a reported accuracy of 82–83% [23]. The accuracy values reported in previous studies for classifying healthy control subjects versus neurological patients [24] are slightly higher than those reported in this study, which is to be expected as there are larger differences between healthy subjects and patients with neurological diseases/disorders than between patients with comparable disease states. Moreover, our predictive model was slightly biased towards the PD class; however, given a large sample size in the PD group, it is logical that the classification accuracy for PD was better than that for AD in the external test data. The reason why the training and test sets have different accuracy rates, especially in AD, is as listed below.

Confirmed diagnosis is carried out by not only SPECT images but also patients' symptoms. In particular, in the case of AD, since only dementia symptoms are typically present, the general medical interview results are significant for the confirmed diagnosis. Since SPECT has no such information, AD might be more difficult to classify by this method alone. In the near future, artificial intelligence diagnosis support using general medical information including images, symptoms, and medical history, will be realized.

In this study, we first applied a one-sided *t*-test to extract voxels that showed large differences between AD and PD patient groups. After extraction, we selected voxels by a step-up procedure method (show Figure 2). The reason that a step-up procedure method was used as the second-step feature selection was that the method can evaluate not only single features, but also features' combinations. One problem than can arise when using a step-up procedure method is that a model might plunge into a local minimum. However, since our accuracy rate of LOO-CV was 98.1% in this study, the step-up procedure method was appropriate.

In a previous study [25], patients with early-stage disease were close to the decision boundary between healthy control and disease status in a Fisher's discrimination analysis model. In our study, some AD and PD cases were also located near the threshold. Since it can be hypothesized that these cases may have had features of both AD and PD, in future studies, we intend to analyze and validate the relationship between probability model results and clinical presentation.

It should be noted that the prediction model selected in this study included both early and delayed image regions. Accordingly, we emphasize that delayed images can provide useful information alone or in combination with early images. Using this approach, we provided not only classification results but also the likelihoods of classifications. Even though this study was not sufficiently able to evaluate the applicability of likelihood values, this model is considered to provide useful information to the end user. As we mentioned above, PD patients sometimes associate AD-like symptoms [11], which indicates early SPECT detections of such patients show the images having both AD and PD features. Hence, when we used only early images, accuracy rate was less than the cases which used both early and delayed images. This indicates that blood flow does not give sufficient information but the absorbed RI tracer by nerve cells has remained information. Thus, we can state that using both early and delayed images is significant to give the

most correct diagnosis possible.

Finally, our model was based on Japanese patients. To our knowledge, few models have been created for Japanese patients only. Because insurance cannot be applied for the use of ^{18}F -FDG PET to the diagnose dementia, SPECT has become more widely used in Japan than in other countries. Thus, our model for discriminating AD from PD in a Japanese population by using SPECT images is clinically meaningful.

4.2 Important regions detected

In this study, the following regions were identified as important for the discrimination of AD from PD using our SVM model: the temporal, sub-lobar, parietal, limbic, and frontal areas exhibited decreased rCBF in patients with AD, whereas the frontal, anterior, parietal, and occipital areas exhibited decreased rCBF in patients with PD. In previous studies, decreases in rCBF as judged by physicians have been reported in the cingulate gyrus, precuneus [26, 27], and temporoparietal region [28] in patients with AD, and in the parietal lobe [25] and posterior parieto-occipital region [29] in patients with PD/dementia. Thus, the regions highlighted by the step-up procedure method in this study are highly consistent with previous physician-based reports. Attempts to identify important brain regions for the disease classification based on MRI have been reported. Chen et al. used SVM to classify scale invariant feature transform features and reported that the limbic lobe, frontal lobe, and sub-lobar area were highly predictive brain regions in both AD and PD [30]. The same regions were selected in this report using SPECT imaging.

Since patients were not compared with healthy control subjects in this study, direct comparisons between our results and previous studies using healthy control subjects need further discussion. Instead, our study identified important regions for diagnostic classification. Heron et al. reported that there were no significant differences in rCBF values between patients with AD and those with PD on arterial spin labeling magnetic resonance imaging [11]. In our study, reductions in rCBF were identified in the frontal and parietal lobes (same regions, but different voxels) of both AD and PD cases. These data suggest that differences in rCBF between AD and PD are localized to small areas rather than generalized regions.

5. Conclusion

In this study, we applied the SVM classification method to SPECT data in order to discriminate individuals with AD from those with PD. Our results suggest that AD and PD can be classified in accordance with SPECT imaging data using a SVM, and that probabilistic assessments are beneficial for SVM classification. The prediction model selected in our proposed method included both early and delayed images. It is therefore suggested that delayed SPECT imaging can provide diagnostically useful information in combination with early SPECT imaging.

Acknowledgement

We would like to thank Y. Zhou for reading this manuscript and providing helpful suggestions as well as Editage (www.editage.jp) for English language editing. This work was supported by JSPS KAKENHI Grant Number JP25870406.

References

- [1] World Alzheimer Report 2016; Alzheimer's Disease International <https://www.alz.co.uk/research/world-report-2016> (accessed Jun 20, 2017).
- [2] WHO; Dementia <http://www.who.int/mediacentre/factsheets/fs362/en/> (accessed Jun 20, 2017).
- [3] GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, Regional, and National Incidence, Prevalence, and Years Lived with Disability for 310 Diseases and Injuries, 1990-2015: A Systematic Analysis for the Global Burden of Disease Study 2015. *Lancet* **2016**, 388 (10053), 1545-1602.
- [4] Machida, K. Comparison between cerebral blood flow SPECT and magnetic resonance imaging for diagnosis of dementia, and multicenter inter-reader variability. *Jap. J. Nucl. Med.* **2010**, 40 (1), 54-56. (in Japanese)
- [5] Ramírez, J.; Górriz, J. M.; Segovia, F.; Chaves, R.; Salas-Gonzalez, D.; *et al.* Computer Aided Diagnosis System for the Alzheimer's Disease Based on Partial Least Squares and Random Forest SPECT Image Classification. *Neurosci. Lett.* **2010**, 472 (2), 99-103.
- [6] López, M.; Ramírez, J.; Górriz, J. M.; Álvarez, I.; Salas-Gonzalez, D.; *et al.* Principal Component Analysis-Based Techniques and Supervised Classification Schemes for the Early Detection of Alzheimer's Disease. *Neurocomputing* **2011**, 74 (8), 1260-1271.
- [7] Padilla, P.; Lopez, M.; Gorriz, J. M.; Ramirez, J.; Salas-Gonzalez, D.; Alvarez, I. NMF-SVM Based CAD Tool Applied to Functional Brain Images for the Diagnosis of Alzheimer's Disease. *IEEE Transactions on Medical Imaging* **2012**, 31 (2), 207-216.
- [8] Ramírez, J.; Górriz, J. M.; Salas-Gonzalez, D.; Romero, A.; López, M.; *et al.* Computer-Aided Diagnosis of Alzheimer's Type Dementia Combining Support Vector Machines and Discriminant Set of Features. *Information Sciences* **2013**, 237, 59-72.
- [9] Harper, L.; Fumagalli, G. G.; Barkhof, F.; Scheltens, P.; O'Brien, J. T.; *et al.* MRI Visual Rating Scales in the Diagnosis of Dementia: Evaluation in 184 Post-Mortem Confirmed Cases. *Brain* **2016**, 139 (4), 1211-1225.
- [10] Aarsland, D.; Kurz, M. W. The Epidemiology of Dementia Associated with Parkinson's Disease. *Brain Pathol.* **2010**, 20 (3), 633-639.
- [11] Le Heron, C. J.; Wright, S. L.; Melzer, T. R.; Myall, D. J.; MacAskill, M. R.; *et al.* Comparing Cerebral Perfusion in Alzheimer's Disease and Parkinson's Disease Dementia: An ASL-MRI Study. *J. Cereb. Blood Flow Metab.* **2014**, 34 (6), 964-970.
- [12] Kim, Y-D.; Jeong, H. S.; Song, I-U.; Chung, Y-A.; Namgung, E.; Kim, Y-D. Brain perfusion alterations in depressed patients with Parkinson's disease. *Ann. Nucl. Med.* **2016**, 30, 731-737. doi:10.1007/s12149-016-1119-2
- [13] Compta, Y.; Parkkinen, L.; O'Sullivan, S. S.; Vandrovcova, J.; Holton, J. L.; *et al.* Lewy- and Alzheimer-Type Pathologies in Parkinson's Disease Dementia: Which Is More Important? *Brain* **2011**, 134 (Pt 5), 1493-1505.
- [14] Halliday, G. M.; Leverenz, J. B.; Schneider, J. S.; Adler, C. H. The Neurobiological Basis of Cognitive Impairment in Parkinson's Disease. *Mov. Disord.* **2014**, 29 (5), 634-650.
- [15] Klöppel, S.; Stonnington, C. M.; Chu, C.; Draganski, B.; Scallan, R. I.; *et al.* Automatic Classification of MR Scans in Alzheimer's Disease. *Brain* **2008**, 131 (Pt 3), 681-689.
- [16] Vandenberghe, R.; Nelissen, N.; Salmon, E.; Ivanoiu, A.; Hasselbalch, S.; *et al.* Binary Classification of 18F-Flutemetamol PET Using Machine Learning: Comparison with Visual Reads and Structural MRI. *NeuroImage* **2013**, 64 (Supplement C), 517-525.
- [17] Platt, J. C. Probabilistic Outputs for Support Vector Machines and Comparisons to Regularized Likelihood Methods. In *ADVANCES IN LARGE MARGIN CLASSIFIERS*; MIT Press, **1999**; pp 61-74.

- [18] Lancaster, J. L.; Rainey, L. H.; Summerlin, J. L.; Freitas, C. S.; Fox, P. T.; *et al.* Automated Labeling of the Human Brain: A Preliminary Report on the Development and Evaluation of a Forward-Transform Method. *Hum. Brain Mapp.* **1997**, 5 (4), 238-242.
- [19] Lancaster, J. L.; Woldorff, M. G.; Parsons, L. M.; Liotti, M.; Freitas, C. S.; *et al.* Automated Talairach Atlas Labels for Functional Brain Mapping. *Hum. Brain Mapp.* **2000**, 10 (3), 120-131.
- [20] Vapnik, V.; Lerner, A. Pattern recognition using generalized portrait method. *Autom. Remote Control* **1963**, 24, 774-780.
- [21] Huertas-Fernández, I.; García-Gómez, F. J.; García-Solís, D.; Benítez-Rivero, S.; Marín-Oyaga, V. A.; *et al.* Machine Learning Models for the Differential Diagnosis of Vascular Parkinsonism and Parkinson's Disease Using [¹²³I] FP-CIT SPECT. *Eur. J. Nucl. Med. Mol. Imaging* **2015**, 42 (1), 112-119.
- [22] Yang, S.-T.; Lee, J.-D.; Chang, T.-C.; Huang, C.-H.; Wang, J.-J.; *et al.* Discrimination between Alzheimer's Disease and Mild Cognitive Impairment Using SOM and PSO-SVM. *Comput. Math. Methods Med.* **2013**, 2013, 253670.
- [23] Westman, E.; Simmons, A.; Zhang, Y.; Muehlboeck, J.-S.; Tunnard, C.; *et al.* Multivariate Analysis of MRI Data for Alzheimer's Disease, Mild Cognitive Impairment and Healthy Controls. *Neuroimage* **2011**, 54 (2), 1178-1187.
- [24] Mak, H. K. F.; Chan, Q.; Zhang, Z.; Petersen, E. T.; Qiu, D.; *et al.* Quantitative Assessment of Cerebral Hemodynamic Parameters by QUASAR Arterial Spin Labeling in Alzheimer's Disease and Cognitively Normal Elderly Adults at 3-Tesla. *J. Alzheimers Dis.* **2012**, 31 (1), 33-44.
- [25] Stühler, E.; Platsch, G.; Weih, M.; Kornhuber, J.; Kuwert, T.; Merhof, D. Multiple Discriminant Analysis of SPECT Data for Alzheimer's Disease, Frontotemporal Dementia and Asymptomatic Controls. In *2011 IEEE Nuclear Science Symposium and Medical Imaging Conference (NSS/MIC)*; **2011**; pp 4398-4401.
- [26] Firbank, M. J.; Colloby, S. J.; Burn, D. J.; McKeith, I. G.; O'Brien, J. T. Regional Cerebral Blood Flow in Parkinson's Disease with and without Dementia. *Neuroimage* **2003**, 20 (2), 1309-1319.
- [27] Hirao, K.; Ohnishi, T.; Hirata, Y.; Yamashita, F.; Mori, T.; *et al.* The Prediction of Rapid Conversion to Alzheimer's Disease in Mild Cognitive Impairment Using Regional Cerebral Blood Flow SPECT. *Neuroimage* **2005**, 28 (4), 1014-1021.
- [28] Petrella, J. R.; Coleman, R. E.; Doraiswamy, P. M. Neuroimaging and Early Diagnosis of Alzheimer Disease: A Look to the Future. *Radiology* **2003**, 226 (2), 315-336.
- [29] Melzer, T. R.; Watts, R.; MacAskill, M. R.; Pearson, J. F.; Rüeger, S.; *et al.* Arterial Spin Labelling Reveals an Abnormal Cerebral Perfusion Pattern in Parkinson's Disease. *Brain* **2011**, 134 (Pt 3), 845-855.
- [30] Chen, Y.; Storrs, J.; Tan, L.; Mazlack, L. J.; Lee, J.-H.; Lu, L. J. Detecting Brain Structural Changes as Biomarker from Magnetic Resonance Images Using a Local Feature Based SVM Approach. *J. Neurosci. Methods* **2014**, 221, 22-31.