Accurate discrimination of Alzheimer's disease from other dementia and/or normal subjects using SPECT specific volume analysis

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ABSTRACT

Discrimination between Alzheimer's disease and other dementia is clinically significant, however it is often difficult. In this study, we developed classification models among Alzheimer's disease (AD), other dementia (OD) and/or normal subjects (NC) using patient factors and indices obtained by brain perfusion SPECT. SPECT is commonly used to assess cerebral blood flow (CBF) and allows the evaluation of the severity of hypoperfusion by introducing statistical parametric mapping (SPM). We investigated a total of 150 cases (50 cases each for AD, OD, and NC) from Tokai University Hospital, Japan. In each case, we obtained a total of 127 candidate parameters from: (A) 2 patient factors (age and sex), (B) 12 CBF parameters and 113 SPM parameters including (C) 3 from specific volume analysis (SVA), and (D) 110 from voxel-based analysis stereotactic extraction estimation (vbSEE). We built linear classifiers with a statistical stepwise feature selection and evaluated the performance with the leave-one-out cross validation strategy. Our classifiers achieved very high classification performances with reasonable number of selected parameters. In the most significant discrimination in clinical, namely those of AD from OD, our classifier achieved both sensitivity (SE) and specificity (SP) of 96%. In a similar way, our classifiers achieved a SE of 90% and a SP of 98% in AD from NC, as well as a SE of 88% and a SP of 86% in AD from OD and NC cases. Introducing SPM indices such as SVA and vbSEE, classification performances improved around 7-15%. We confirmed that these SPM factors are quite important for diagnosing Alzheimer's disease.

Keywords: Alzheimer's disease, SPECT, SVA, vbSEE

1. INTRODUCTION

Dementia has a wide variety of causative diseases and often shows atypical symptoms and therefore diagnosis of dementia is usually difficult. Alzheimer's disease is best known and the most common type of dementia and the number of incidents are estimated 5.4 million in United States in 2012.[1] Almost one in eight people age 65 and older has Alzheimer's disease and nearly half of people age 85 and older have it. Alzheimer's disease has become the sixth-leading cause of death so far. Since development of specific therapy for Alzheimer 's disease have been actively made, accurate diagnosis between Alzheimer's disease and other dementia and/or normal subjective is quite important. In diagnosis, clinical information and symptom(s) are firstly investigated and imaging modalities such as MRI, PET and SPECT are supplementarily used if necessary. MRI provides the severity and regions of brain atrophy, PET visualizes the deposited specific substances, referred to as amyloid imaging etc., and SPECT enable us to monitor the distribution of cerebral blood flow (CBF). Images obtained from those modalities greatly help in diagnosing dementia, however diagnosis highly depends on physician's experience and is therefore subjective. Recently, new objective diagnosis scheme using SPECT was developed and reported they help to make objective diagnosis. It is generally called statistical parametric mapping (SPM).

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Table 1. Parameter candidates

category		#p †	description	value type
A	clinical	2	age, sex	absolute
B	conventional SPECT	12	· CBF values (CBF) in 4 areas: (left(L), right (R), overall (A), left-to-right asymmetry (Asy))	absolute
			· decrease of CBF (∇CBF) in 6 areas: (frontal(F), temporal(T), parietal(P), overall cortex (A), sensory-motor area (S))	score[1:3]
			· difference of CBF (δCBF) in 2 sides:	
			left and right (L-R)	score[0:2]
			front and back (F-B)	score[0:5]
C	SVA	3	severity, extent, ratio	z-score
D	vbSEE level3	110	severity in 55 lobules extent in 55 lobules	z-score

†: #p: Number of parameter candidates in the category.

The easy Z-score Imaging system (eZIS) is one of the techniques based on SPM.[2] The eZIS represents the distribution of CBF in z-score (i.e. zero mean and unit variance) and it is mapped into the standard brain. Accordingly, radiologists can easily compare original SPECT and eZIS images in the same geometry regardless of the shape of the individual brain. Based on the eZIS, further advanced applications have been developed. Representative analyses are specific volume of interest analysis (SVA)[3,4] and voxel-based analysis stereotactic extraction estimation (vbSEE).[5]

The SVA represents the degree of CBF in early Alzheimer's disesase-specific involved areas in a part of the parietal lobe and it offers three indices such as the severity, extent, and ratio. The vbSEE is the technique to automatically extract the regional z-scores in pre-defined analyze levels of the brain areas such as each hemisphere, lobes, lobules, and Broadmann's areas.

In this paper, we developed classfication models among Alzheimer's disease (AD), other dementia (OD) and/or normal subjects (NC) with and without those sophisticated SPECT indices and compared the classification performances. The primary objective of this study was to develop accurate classifiers among those categories and the second is to investigate the incremental diagnostic value of the above new indices.

2. MATERIAL AND METHOD

We investigated a total of 150 cases (50 cases each for AD, OD, and NC) from Tokai University Hospital, Japan. Distribution of patients' are 71.5±7.8, 74.4±8.0, and 70.6±7.8 years old (mean±SD) in AD, OD, and NC cases, respectively.

From each case, we obtained a total of 127 candidate parameters such as: (A) 2 clinical factors (age and sex), (B) 12 CBF parameters from SPECT, (C) 3 parameters from specific volume analysis (SVA), and (D) 110 parameters from voxel-based analysis stereotactic extraction estimation (vbSEE). The detailed breakdown is shown in Table 1.

Two clinical and four SPECT parameters (CBF values) were described in the absolute value. The asymmetry of CBF between left and right, CBF_{Asy} is defined by the following equation:

$$CBF_{Asy} = 2 \cdot \frac{|CBF_L - CBF_R|}{CBF_L + CBF_R}. \quad (1)$$

Remaining eight SPECT parameters were represented in the scored value rated by radiologists. Six ∇CBF values reflecting the decrease of CBF were expressed by using a 3-point scoring system (1: mild, 2: moderate, and 3: severe decrease). The difference of CBF between the left and right sides (δCBF_{L-R}) was scored in [0,2]

(0: normal, 1: moderate, 2:large difference), and that between front and back (δCBF_{F-B}) was evaluated in [0,5] (1: front-dominant hypoperfusion, ⋯, 3: balanced, ..., 5: back-predominant hypoperfusion). Note that patients with Alzheimer's disease tend to show larger decrease of CBF in the back areas and accordingly have higher scores.

In the SVA, the severity indicates the mean of the z-score in voxels yielding the z-score exceeding 0 in the early Alzheimer's disease-specific region. The extent is the percentage of voxels with the z-score equal to or exceeding 2.0 in the specific region. The ratio means the specific region-to-the entire brain ratio of the percentage of voxels with the z-score equal to or exceeding 2.0.

In the vbSEE, analytical level can be set to hemi-sphere (level 1: 2 regions), lobus (level 2: 12 regions), lobule (level 3: 55 regions), and Broadman's areas (level 5: 52 regions). In the defined analytical level, vbSEE calculates the severity and the extent in each region. Note that these scores are represented in the z-score.

In this study, we selected vbSEE level 3 (110 parameters: 55 lobules x 2 (severity and extent) according to the results of preliminary experiments. Table 2 summarizes the correspondence of the locations of lobules and parameter numbers used in this study.

Table 2. Correspondence table of lobules and their parameter numbers used in this study

lobules	extent	severity	lobules	extent	severity
Angular Gyrus	1	2	Middle Temporal Gyrus	57	58
Abterior Cingulate	3	4	Nodule	59	60
Caudate	5	6	Orbital Gyrus	61	62
Cerebellar Lingual	7	8	Paracentral Lobule	63	64
Cerebellar Tonsil	9	10	Parahippocampal Gyrus	65	66
Cingulate Gyrus	11	12	Postcentral Gyrus	67	68
Claustrum	13	14	Posterior Cingulate	69	70
Culmen	15	16	Precentral Gyrus	71	72
Culmen of Vermis	17	18	Precuneus	73	74
Cuneus	19	20	Pyramis	75	76
Declive	21	22	Pyramis of Vermis	77	78
Declive of Vermis	23	24	Rectal Gyrus	79	80
Extra-Nuclear	25	26	Subcallosal Gyrus	81	82
Fastigium	27	28	Sub-Gyral	83	84
Fourth Ventricle	29	30	Superior Frontal Gyrus	85	86
Fusiform Gyrus	31	32	Superior Occipital Gyrus	87	88
Inferior Frontal Gyrus	33	34	Superior Parietal Lobule	89	90
Inferior Occipital Gyrus	35	36	Superior Temporal Gyrus	91	92
Inferior Parietal Lobule	37	38	Supramarginal Gyrus	93	94
Inferior Semi-Lunar Lobule	39	40	Thalamus	95	96
Inferior Temporal Gyrus	41	42	Third Ventricle	97	98
Insula	43	44	Transverse Temporal Gyrus	99	100
Lateral Ventricle	45	46	Tuber	101	102
Lentiform Nucleus	47	48	Tuber of Vermis	103	104
Lingual Gyrus	49	50	Uncus	105	106
Medial Frontal Gyrus	51	52	Uvula	107	108
Middle Frontal Gyrus	53	54	Uvula of Vermis	109	110
Middle Occipital Gyrus	55	56			

3. MODEL DEVELOPMENT AND EVALUATION CRITERIA

We built linear classifiers to discriminate AD, OD and NC classes, respectively. More concretely, we developed following classifiers considering the medial significance: (1) AD vs OD, (2) AD vs NC, and (3) AD+OD vs NC.

In order to evaluate the effectiveness of newly introduced parameters, such as SVA and/or vbSEE, we generated classifiers in each category with the parameter candidates such as (i) basic parameters (A+B: 14 parameters), (ii) basic+SVA (A+B+C: 17 parameters), and (iii) all parameters (A+B+C+D: 127 parameters) and compared their diagnostic performances.

Feature selection is one of the most important steps for developing a classifier. The parameters used in each regression model were selected by an incremental stepwise method which determines the statistically most significant input parameters in a sequential manner.[6] The detailed procedures are in followings:

1. Let the all parameters $\mathbf{x} \in \mathbf{R^{127}}$. Set the selected parameter SP to NULL and their number $\#_{SP} = 0$.
2. Search for one input parameter x^* from $\mathbf{x}$ where the regression model with x^* yields the best performance (lowest residual). Add SP to x^* and $\#_{SP} = 1$.
3. Build linear regression models whose input elements are SP and x' without redundancy ($\forall x' \subset \mathbf{x}$, number of input is $\#_{SP}+1$) and select one input parameter x'^* which has the highest partial correlation coefficient among x'.
4. Calculate the variance ratio (F-value) between the regression sum of squares and the residual sum of squares of the built regression model.
5. Perform statistical F-test (calculate p value) in order to verify that the model is reliable.
   If $p < 0.05$: $SP \leftarrow SP + x'^*$, $\#_{SP} \leftarrow \#_{SP} + 1$ and return to Step 3.
   Else if $0.05 \leq p < 0.10$: discard x'^* and return to Step 3 and find the next best candidate.
   Else if the developed model has a statistically negligible parameter $x^\dagger (0.10 \leq p)$ among the currently selected inputs, reject $x^\dagger$ from SP, $\#_{SP} \leftarrow \#_{SP} - 1$ and return to Step 3.
   Otherwise terminate the feature selection process.

Sensitivity (SE) and specificity (SP) were used as the evaluation criteria for diagnostic accuracy. We also plotted the receiver operating characteristic (ROC) curve to examine the performance of the classifier under varying conditions. The diagnostic performance was also quantified by the area under the ROC curve (AUC) measure. Note here that since the number of the available size of data is limited, the classification performance was evaluated with the leave-one-out cross validation strategy.

4. RESULTS

The classification performances between (1) AD vs OD, (2) AD vs NC, and (3) AD+OD vs NC, and their requisite parameters selected by the feature selection were summarized in Tables 3, 4 and 5, respectively. As for (D) vbSEE parameters, please refer to Table 2 for detail. Here, #p represents the number of selected parameters.

In tables, SE and SP were the values at the threshold where the product of the SE and SP was maximum. We can see our classification models achieve good classification performance. In the most significant discrimination in clinical, namely those of AD from OD, our classifier achieved both sensitivity (SE) and specificity (SP) of 96% and the AUC of 0.989 (see Table 3).

5. DISCUSSION

Sophisticated parameters improved the classification performance around 7-15 % in AUC. The effectiveness of (C) SVA was significant considering the balance of the number of additional parameters and the performance improvement. In (D) vbSEE, z-scores of subsites of parietal and occipital lobes (2, 56 and 73), the sensory-motor cortex and neighborhood (53 and 72), and the lentiform nucleus and nearby areas (14, 44 and 47) were mainly selected, and classification performances improved. In all classification tasks, the effectiveness of (D) vbSEE was also confirmed and it especially improved 8.7% in classification between AD and OD. This is mainly due to the improvement of the separation of Alzheimer's disease and the dementia with Lewy bodies. Since both of these diseases show posterior-dominant hypoperfusion in brain SPECT, it is difficult to separate them by using the SVA whose regions of interest are limited to a part of the parietal lobe.

In this study, the number of available cases was limited to 150. We used linear regression models to discriminate Alzheimers' cases from the others. More sophisticated classifiers such as support vector machine classifiers have been used successfully in a wide variety of applications, but using a linear regression models provides us high enough classification performance under the limited situation and they enable us to observe the siginificant parameters directly. The number of selected parameters was relatively large when (D) vbSEE was introduced. We are going to investigate and test with larger dataset in the near future.

6. CONCLUSIONS

In this paper, we developed classification models for Alzheimer's disease (AD) from other dementia (OD) and/or normal subjects (NC) with and without sophisticated SPECT indices such as specific volume analysis (SVA), and voxel-based analysis stereotactic extraction estimation (vbSEE). With the aid of these indices, our classifiers achieved very high classification accuracy of 0.989 in AUC in discriminating AD from OD cases and this is almost 12% better than classifier built with only conventional factors. Although there is a limitation on the size of dataset, we confirmed that the introducing abovementioned indices improved the diagnostic accuracy.

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REFERENCES

[1] Alzheimer's Association, "2012 Alzheimer's disease facts and figures," Alzheimer's & Dementia, Volume 8, issue 2, (2012).

[2] Matsuda H, Mizumura S, Soma T, Takemura N., "Conversion of brain SPECT images between different collimators and reconstruction processes for analysis using statistical parametric mapping," Nucl Med Commun. Jan; 25(1),67-74 (2004).

[3] Matsuda H, Mizumura S, Nagao T, Ota T, Iizuka T, Nemoto K, Takemura N, Arai H, and Homma A, "Automated Discrimination Between Very Early Alzheimer Disease and Controls Using an Easy Z-Score Imaging System for Multicenter Brain Perfusion Single-Photon Emission Tomography," AJNR Am J Neuroradiol April 28, 731-736 (2007).

[4] Waragai M, Mizumura S, Yamada T, and Matsuda H.,"Differentiation of Early-Stage Alzheimer's Disease from Other Types of Dementia Using Brain Perfusion Single Photon Emission Computed Tomography with Easy Z-Score Imaging System Analysis," Dement Geriatr Cogn Disord, 26, 547-555 (2008).

[5] Uruma G, Kakuda W, Abo M, "Changes in regional cerebral blood flow in the right cortex homologous to left language areas are directly affected by left hemispheric damage in aphasic stroke patients: evaluation by Tc-ECD SPECT and novel analytic software," Eur J Neurol, 17(3), 461-469 (2010).

[6] Everitt BS, Dunn G., "Applied multivariate data analysis," London, Edward Arnold, 219-220 (1991).

Table 3. Classification performance between AD and OD using leave-one-out cross validation

AD vs OD	SE⋆	SP⋆	AUC †	#p	selected parameters
basic (A,B)	84	82	0.863	4	(B) δCBF_{F-B}, (B) ∇CBF_B, (B) ∇CBF_A, (A) sex
basic+SVA (A,B,C)	88	86	0.902	4	(C) extent, ∇CBF_B, δCBF_{F-B}, (A) sex
basic+SVA+vbSEE (A,B,C,D)	**96**	**96**	**0.989**	14	(C) extent, (B) ∇CBF_B, (D)47, (D)106, (B) ∇CBF_F, (D)53, (D)79, (D)44, (D)14, (D)2, (B) δCBF_{F-B}, (D)72, (D)73, (D)56

⋆: SE and SP: At the point where the product of the SE and SP was maximum.
†: AUC: area under the ROC curve [0,1].

Table 4. Classification performance between AD and NC using leave-one-out cross validation

AD vs NC	SE⋆	SP⋆	AUC †	#p	selected parameters
basic (A,B)	86	92	0.839	2	(B) ∇CBF_V, (B) CBF_S
basic+SVA (A,B,C)	88	88	0.950	5	(B) ∇CBF_V, (C) ratio, (A) sex, ∇CBF_A, (A) age
basic+SVA+vbSEE (A,B,C,D)	**90**	**98**	**0.984**	9	(B) ∇CBF_V, (D)105, (C) ratio, (D)38, (A) sex, (D)75 (D)45, (D)63, (D)68

⋆: SE and SP: At the point where the product of the SE and SP was maximum.
†: AUC: area under the ROC curve [0,1].

Table 5. Classification performance between AD+OD and NC using leave-one-out cross validation

AD+OD vs NC	SE⋆	SP⋆	AUC †	#p	selected parameters
basic (A,B)	89	86	0.941	5	(B) ∇CBF_V, (B) ∇CBF_F, (A) age, (B) δCBF_{L-R} (B) CBF_{Asy}
basic+SVA (A,B,C)	88	92	0.941	5	(B) ∇CBF_V, (B) ∇CBF_F, (A) age, (B) δCBF_{L-R} (C) ratio
basic+SVA+vbSEE (A,B,C,D)	**92**	**94**	**0.970**	10	(B) ∇CBF_V, (D)25, (D)75, (D)12, (D)52, (B) δCBF_{L-R}, (D)74, (C)ratio, (D)24, (D)80

⋆: SE and SP: At the point where the product of the SE and SP was maximum.
†: AUC: area under the ROC curve [0,1].