Original Article
Diagnostic performance of an automated analysis software for the diagnosis of Alzheimer's dementia with ^{18}F FDG PET

Sasan Partovi[1], Roger Yuh[1], Sara Pirozzi[2], Ziang Lu[1], Spencer Couturier[1], Ulrich Grosse[1], Mark D Schluchter[3], Aaron Nelson[2], Robert Jones[1], James K O'Donnell[1], Peter Faulhaber[1]

[1]Department of Radiology, University Hospitals Cleveland Medical Center, Case Western Reserve University, Cleveland, Ohio; [2]MIM Software Inc., Cleveland, Ohio; [3]Department of Biostatistics and Epidemiology, Case Western Reserve University, Cleveland, Ohio

Abstract: The objective of this study was to assess the ability of a quantitative software-aided approach to improve the diagnostic accuracy of ^{18}F FDG PET for Alzheimer's dementia over visual analysis alone. Twenty normal subjects (M:F-12:8; mean age 80.6 years) and twenty mild AD subjects (M:F-12:8; mean age 70.6 years) with ^{18}F FDG PET scans were obtained from the ADNI database. Three blinded readers interpreted these PET images first using a visual qualitative approach and then using a quantitative software-aided approach. Images were classified on two five-point scales based on normal/abnormal (1-definitely normal; 5-definitely abnormal) and presence of AD (1-definitely not AD; 5-definitely AD). Diagnostic sensitivity, specificity, and accuracy for both approaches were compared based on the aforementioned scales. The sensitivity, specificity, and accuracy for the normal vs. abnormal readings of all readers combined were higher when comparing the software-aided vs. visual approach (sensitivity 0.93 vs. 0.83 P = 0.0466; specificity 0.85 vs. 0.60 P = 0.0005; accuracy 0.89 vs. 0.72 P<0.0001). The specificity and accuracy for absence vs. presence of AD of all readers combined were higher when comparing the software-aided vs. visual approach (specificity 0.90 vs. 0.70 P = 0.0008; accuracy 0.81 vs. 0.72 P = 0.0356). Sensitivities of the software-aided and visual approaches did not differ significantly (0.72 vs. 0.73 P = 0.74). The quantitative software-aided approach appears to improve the performance of ^{18}F FDG PET for the diagnosis of mild AD. It may be helpful for experienced ^{18}F FDG PET readers analyzing challenging cases.

Keywords: PET, Alzheimer's dementia, quantitative, software aided

Introduction

The prevalence of Alzheimer's disease (AD) is continuously increasing in the United States with an expected doubling of the annual number of incident cases in 2050 [1]. Symptoms of the disease include cognitive impairment including memory dysfunction [2]. The diagnosis is most frequently made clinically based on neuropsychological testing, in particular with the Mini Mental Status Examination (MMSE) [3, 4]. However, the MMSE can be of limited value in early forms of dementia and mild cognitive impairment (MCI) [5, 6]. Imaging in the workup of AD is evolving with several neuroimaging modalities applied in clinical settings, including positron emission tomography (PET), single photon emission computed tomography (SPECT), magnetic resonance imaging (MRI) and com-

puted tomography (CT). PET with attenuation correction by low dose CT has been found to be a highly useful imaging modality for the diagnosis of neurodegenerative disorders [7]. According to the Center for Medicare and Medicaid Services, PET imaging with 2-deoxy-2-[[18](F)]fluoro-D-glucose (FDG) is considered an important step in the workup of a patient diagnosed with dementia who is suffering from at least 6 months of documented cognitive decline, has previously been evaluated for alternative degenerative diseases, and met the criteria for both AD and/or frontotemporal dementia (FTD) [8]. FDG as a radiotracer is reflecting glucose metabolism [9] and thus enables depiction of reduced activity of glucose metabolism in affected brain areas of AD [10, 11]. Pattern of abnormalities of cerebral glucose

Table 1. Baseline characteristics of the healthy controls and Alzheimer disease patients from the ADNI database (https://ida.loni.usc.edu)

	Healthy controls	Alzheimer disease patients
Number of subjects	20	20
Male (%)	12 (60)	12 (60)
Mean age ± standard deviation	80.6±7.2*	70.6±10.4*
Mini-Mental State Examination (MMSE) ± standard deviation	29±1.4	22.8±1.9
Clinical Dementia Rating (CDR)	0	0.5/1

*Mean age differed significantly between healthy controls and Alzheimer disease patients (P = 0.005).

metabolism in AD can involve the parietotemporal, posterior cingulate, precuneus and frontal cortex [2, 12-18]. Sparing of the sensorimotor cortex, subcortical gray matter, visual cortex, basal ganglia, cerebellum, and thalami is a distinguishing feature of AD as opposed to other forms of dementia [8]. FDG-PET revealed sensitivity above 90% and specificity above 70% for the diagnosis of AD while correctly identifying the presence of AD in 88% of patients when compared with histopathology [17]. A recently published meta-analysis pooled data from 27 studies and determined a sensitivity of 90% and a specificity of 89% for the diagnosis of AD against non-demented healthy controls with FDG-PET [19]. Interpretation of FDG-PET in the setting AD is usually in a manual approach using visual qualitative reading. A manual approach can be prone to interpretation errors and strongly depends on the experience and training of the reading physician [20]. FDG-PET with a quantitative component using software-aided analysis may increase diagnostic performance for AD detection. Previous studies for quantitative AD diagnosis with FDG-PET applied voxel-based procedures with age-adjusted t-statistics, statistical parametric mapping approaches and standardized stereotactic surface projections (SSPs) [21-23]. The purpose of this study was to determine whether a commercial quantitative software tool, MIMneuro™ (MIM Software Inc. Cleveland, OH) could improve the diagnosis of AD compared to qualitative visual analysis alone for three experienced board certified radiology and nuclear medicine physicians (25 years, 12 years and 6 years of experience).

Subjects and methods

ADNI (Alzheimer's disease neuroimaging initiative)

Forty subjects with FDG PET brain scans were obtained from the ADNI database (adni.loni.

usc.edu). All subjects included within the ADNI database gave written informed consent to participate in the study. The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). For up-to-date information, see www.adni-info.org. In addition to FDG PET scans, all ADNI subjects received baseline comprehensive neuropsychological evaluation, laboratory tests and blood samples for genetic analysis, and structural MR exams [24].

Subject selection

Twenty normal controls and twenty AD subjects were chosen from the ADNI database. The normal control patients (12 male, 8 female) ranged in age from 71 to 94, with a mean age ± SD of 80.6±7.2 y, and fulfilled all eligibility criteria for enrollment as an ADNI normal control including a Clinical Dementia Rating (CDR) score of 0, a MMSE score between 24-30, and no diagnosis of depression, MCI, or dementia. Normal controls included in this study also had a negative PET amyloid scan and did not progress to MCI or AD within 24 month follow up. The mild AD subjects (12 male, 8 female) used in this study had CDR scores of 0.5 or 1, MMSE scores between 20 and 26, and met the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria for probable AD, and had a positive amyloid scan. AD patients ranged in age from 55 to 89 years, with a mean age ± SD of 70.6±10.4 years. Baseline characteristics of healthy controls and AD patients are
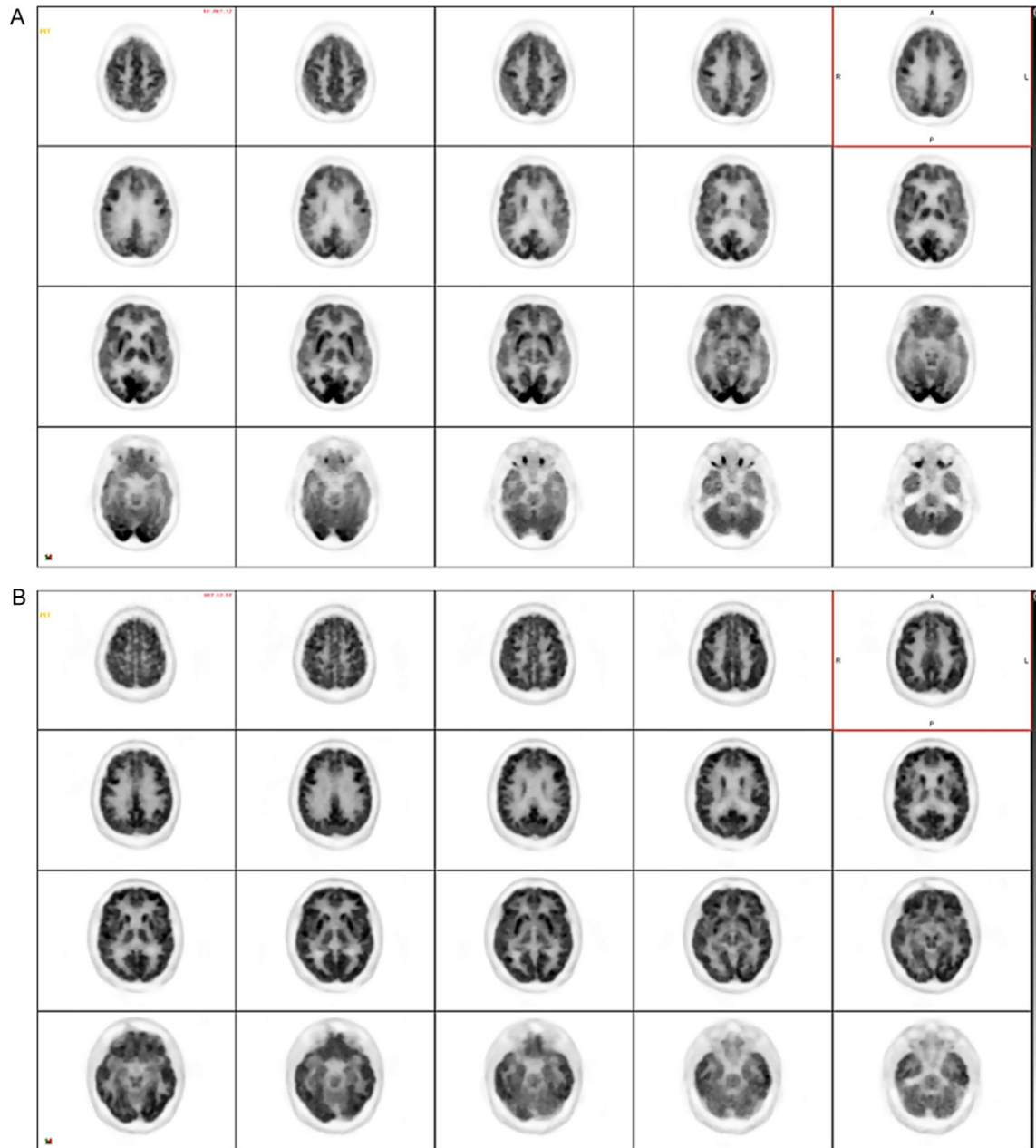
Figure 1. Representative examples of FDG-PET in a patient with Alzheimer's disease (A) and in a healthy control (B) from the ADNI database (https://ida.loni.usc.edu).

shown in **Table 1**. All subjects were clinically followed and imaged at 6, 12, and 24 months.

^{18}F-FDG PET imaging data

All FDG PET scans were acquired between 2007 and 2011 under common standardized FDG PET acquisition protocols consistent with ADNI standards. Data were corrected for scatter and radiation-attenuation using transmis- sion scans for systems having rod sources, or by CT scan for sites with a PET/CT scanner. Data were reconstructed using measured-attenuation correction and image reconstruction algorithms specified for each scanner (http://adni.loni.usc.edu). Raw PET data in DICOM format were first uploaded to the University of Michigan for pre-processing to correct for differences across PET scanners used at various ADNI sites. During preprocess-

Table 2. Sensitivity, specificity and accuracy for normal (1, 2 on the applied scale) vs. abnormal readings (5 on the applied scale) when comparing software-aided vs. manual readings in all three readers and averaged over all readers

Reader	Sensitivity			Specificity			Accuracy		
	Auto	Manual	p-value	Auto	Manual	p-value	Auto	Manual	p-value
1	0.90	0.75		0.85	0.45		0.875	0.600	
2	1.00	0.80		0.95	0.75		0.975	0.775	
3	0.90	0.95		0.75	0.60		0.825	0.775	
Combined	0.933	0.833	0.047	0.85	0.60	0.0005	0.892	0.717	<0.0001

Table 3. Sensitivity, specificity and accuracy for absence (1, 2 on the applied scale) vs. presence (3, 4, 5 on the applied scale) of Alzheimer's disease when comparing software-aided vs. manual readings in all three readers and averaged over all readers

Reader	Sensitivity			Specificity			Accuracy		
	Auto	Manual	p-value	Auto	Manual	p-value	Auto	Manual	p-value
1	0.45	0.65		0.95	0.50		0.70	0.575	
2	0.85	0.70		0.95	0.85		0.90	0.775	
3	0.85	0.85		0.80	0.75		0.825	0.80	
Combined	0.717	0.733	0.74	0.90	0.70	0.0008	0.808	0.717	0.0356

ing, first each of the five-minute emission frames acquired in every FDG scan were co-registered and then averaged to the first frame. The co-registered, averaged image was then reoriented to a common spatial orientation, such that the anterior-posterior axis of the subject ran parallel to the anterior commissure-posterior commissure (AC-PC) line, and interpolated onto a uniform 60×160×96 voxel image grid, with 1.5 mm cubic voxels (http://adni.loni.usc.edu/methods/pet-analysis/pre-processing). Finally a subject-specific mask was applied for intensity normalization (where average in the mask was one). Further details regarding ADNI image acquisition and processing are described in Jagust et al [24].

Visual image interpretation

Pre-processed ADNI images (co-registered, averaged, standardized image and voxel size) were downloaded from the ADNI LONI database in DICOM format (https://ida.loni.usc.edu). Three observers who were blinded to the diagnoses were selected as participants in this study. All three readers were highly experienced US board certified nuclear medicine and radiology physicians (25 years, 12 years and 6 years of experience). Before image interpretation, a 30-minute training session was provided to review the criteria for defining typical metabolic abnormalities for AD on FDG PET brain scans.

The following criteria were used for a visually positive diagnosis of AD: hypometabolism in the temporal and parietal lobes, the posterior cingulate gyrus and the precuneus, with relative sparing of the sensorimotor and primary visual cortices and cerebellum. The striatum and thalamus are also spared. Readers were reminded that in early stages the hypometabolism might appear asymmetric, however, as the disease progresses it will often become bilateral. Bilateral involvement is more common, however, there may still be some of the earlier asymmetry present. With more advanced disease frontal lobe deficits can be seen as well. Occasionally there may be frontal dominant disease where frontal deficits are more prominent than the parietotemporal deficits [12, 25-30].

Prior to actual interpretation sessions, FDG PET images of a healthy subject and an AD subject were shown in a standard three plane display as sample cases to highlight key differences between normal and AD brain scans (**Figure 1**). After the training session, PET images were presented to readers for visual interpretation in a conventional three plane display (axial, sagittal, and coronal) with a standard gray scale over the course of several weeks. Order of normal and AD images were randomized and presented by a non-observer who transcribed patient rankings into an excel spreadsheet. FDG PET images were visually classified using

Table 4. Area under the ROC curves for normal vs. abnormal readings when comparing software-aided vs. manual readings in all three readers and averaged over all readers

Reader	Auto	Manual	*P*-value
1	0.896	0.735	
2	0.994	0.821	
3	0.895	0.833	
Combined	0.978	0.841	0.0154

Table 5. Area under the ROC curves for absence vs. presence of Alzheimer's disease when comparing software-aided vs. manual readings in all three readers and averaged over all readers

Reader	Auto	Manual	*P*-value
1	0.800	0.626	
2	0.956	0.821	
3	0.890	0.884	
Combined	0.943	0.814	0.0264

two rating scales: Normal/Abnormal and AD/No AD. Each reader rated each case on a scale from 1 = definitely normal to 5 = definitely abnormal, and on a scale from 1 = definitely not AD to 5 = definitely AD. For the normal/abnormal scale, a 1 was considered "definitely normal", and a 2 was considered "probably normal". A score of 4 or 5 corresponded to "probably abnormal" and "definitely abnormal", respectively. For the AD/No AD scale rating, a 1 was considered "definitely not AD", and a 2 was considered "probably not AD". A score of 4 or 5 corresponded to "probably AD" and "definitely AD", respectively. For both rating systems a score of 3 was considered equivocal, and counted as positive for both scales. For the normal/abnormal scale this meant a 3 was counted as abnormal, and for the AD/No AD scale this meant a 3 counted as positive for presence of AD. The number of patients that were assigned to each score for Normal/Abnormal AD/No AD and can be observed in **Table 6**. Visual analysis was completed first for all subjects prior to beginning the quantitative analysis portion of the study.

Aided image interpretation

Following visual assessment, quantitative analysis was performed on the same set of 40 FDG PET scans. A non-observer presented images to the three readers who were again asked to rate each case with the additional aid of quantification results generated by MIMneuro. Readers rated the images using the same two scales used for visual assessment (Normal/Abnormal and AD/No AD). All FDG PET brains were first spatially normalized to a standard FDG PET brain template using a 9-parameter affine registration followed by a nonlinear landmark-based deformation. This registration allowed for comparisons to a normal database which had also been registered to the template. The normal database was comprised of 43 healthy controls between the ages of 41-80, with a mean age ± SD of 63.8±10 y. Both the normal comparison set and subject's brains were normalized to the mean activity of the whole brain, pons, and cerebellum before comparison. Statistical comparisons were made between the subject and the normal database for each voxel in the brain. Z scores were calculated from the normalized values for voxel-based analysis using the following formula: $Z = [\text{mean}_{subject} - \text{mean}_{normals}]/\text{SD}_{normals}$.

Stereotactic surface projections (SSPs) were also utilized, providing an overview of cortical FDG uptake. SSPs are obtained by looking for the highest activity voxel along a vector perpendicular to the surface of the brain and projecting that voxel on to the surface [25]. Statistically significant differences were highlighted for all of the voxels in the brain on both the multi-planar reconstructed images and the SSPs. The differences were represented as z-scores or the number of standard deviations away from the mean. Voxels with z-scores <-1.65 were highlighted in a cool color scale on the subject's registered brain (**Figure 2**). A z-score cutoff of -1.65 using a one-tailed t-test corresponds to statistically significant difference from normal at the 0.05 significance level. Processed quantitative results displaying voxel Z scores and SSPs normalized to each reference region were saved into a session, which allowed the software to be restored to a given state (including display layout and quantitative voxel and SSP results) for a consistent presentation to each reader. Cases were re-randomized for the second time to minimize recall bias and presented to readers in the saved session format with the processed quantitative results.

Table 6. The distribution of scores for both normal/abnormal and presence of AD/absence AD parameters. A rating of 3 or higher was considered to be indicative of abnormal/presence of AD

	Normal vs. abnormal			AD vs. no AD		
	Reader 1	Reader 2	Reader 3	Reader 1	Reader 2	Reader 3
Rating of 1	13	18	7	34	23	25
Rating of 2	20	20	23	13	22	12
Rating of 3	6	1	6	7	1	6
Rating of 4	12	14	15	10	12	19
Rating of 5	29	27	29	16	22	18

Statistical analysis

Accuracy of visual and aided readings were compared for the Normal/Abnormal scale, and also for the AD/No AD scale. Receiver operating characteristic (ROC) analysis was performed to determine diagnostic accuracy. ROC curves were estimated by method (visual, aided) for each scale (Normal/Abnormal and AD/No AD) for each reader, and using the average rating across the three readers. Nonparametric estimates of ROC curve areas were estimated and compared between methods using a non-parametric approach, implemented in the Proc Logistic procedure of SAS version 9.4 (SAS Institute, Inc., Cary, NC). A generalized estimating equations logistic regression model was used to compare sensitivity, specificity, and accuracy of aided vs. visual methods using data from all three readers where readings of 3 or higher on the 5-point scale were considered positive/abnormal, and readings of 1-2 were considered negative/normal.

Results

Representative example FDG-PET scans acquired from the ADNI database are shown for an AD patient and healthy control in **Figure 1**. SSPs with overlaid z-scores for a healthy control and AD patient using MIMneuro is demonstrated in **Figure 2**. The distribution of scores for both the visual and software-aided approaches is listed in **Table 6**.

Sensitivity, specificity and accuracy for software-aided vs. manual readings

When comparing the normal (1, 2 on the applied scale) vs. abnormal readings (3, 4, 5 on the applied scale) observed specificity and accuracy were consistently higher throughout all three readers when using the software-aided

approach and observed sensitivity of the software-aided approach was higher for two out of three readers. When combining the results of all readers the sensitivity, specificity and accuracy increased when using the aided approach vs. the visual approach. Accuracy, specificity and sensitivity reached significance level for all three metrics (P = 0.0466, P = 0.0005, P<0.0001 respectively). The results are listed in **Table 2**.

When comparing absence (1, 2 on the applied scale) vs. presence (3, 4, 5 on the applied scale) of AD observed specificity and accuracy were consistently higher for each of the three readers when using the software-aided approach. Observed sensitivity was higher in reader 2, equal in reader 3, and was lower in reader 1 when using the aided vs. the visual approach. When combining the results of all readers the specificity and accuracy were significantly increased (P = 0.0008 and P = 0.0356) when using the software-aided approach vs. visual inspection alone. Sensitivities of the software-aided and visual approaches did not differ significantly (0.72 vs. 0.73 P = 0.74). The results are listed in **Table 3**.

ROC curves for software-aided vs. manual readings

For the ROC analyses using combined data from all three readers, the area under the ROC curve was higher when using software-aided vs. visual readings, both for normal vs. abnormal readings (P = 0.0154), and for absence vs. presence of AD readings (P = 0.0264). The results of each reader and combined are listed in **Table 4** (normal vs. abnormal readings) and **Table 5** (absence vs. presence readings of Alzheimer's disease). The ROC curve using the average of all three readers along with the ROC associated statistics comparing software-aided vs. visual readings is shown in **Figure 3** for normal vs. abnormal readings and in **Figure 4** for absence vs. presence readings of AD.

Discussion

In this study, we aimed to show the effect of a quantitative software-aided approach for the diagnosis of early stage AD with ^{18}F FDG PET. The MIMneuro software-aided approach demonstrated an improvement of AD diagnostic specificity and accuracy while maintaining similar sensitivity compared to the qualitative visu-
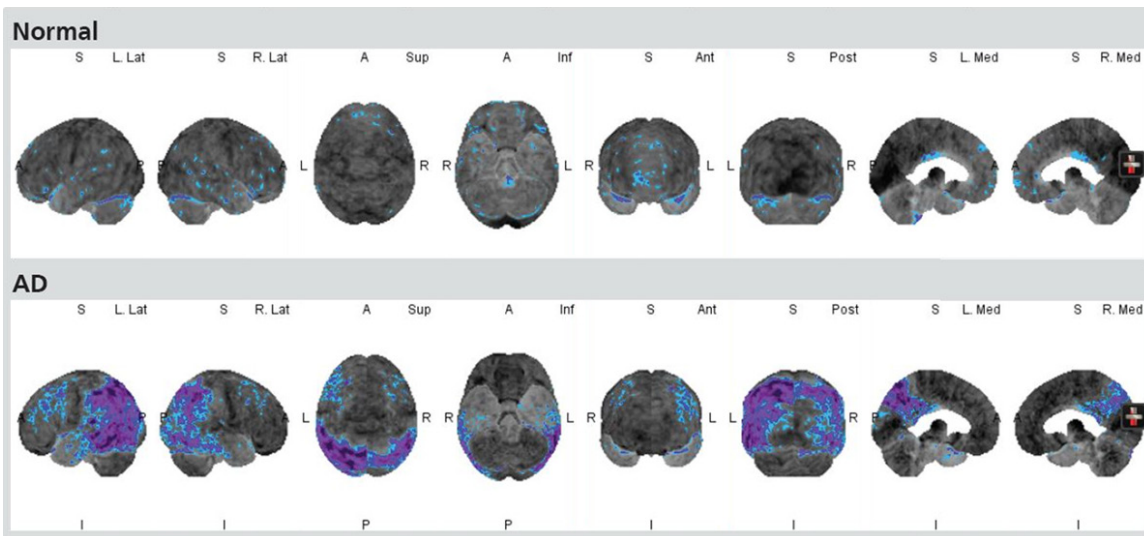
Figure 2. Stereotactic surface projections (SSPs) of a healthy control and Alzheimer's disease patient. Statistically significant areas of hypometabolism are highlighted in blue (z-score <-1.65). Note the pattern of hypometabolism is consistent with Alzheimer's disease in the second row.
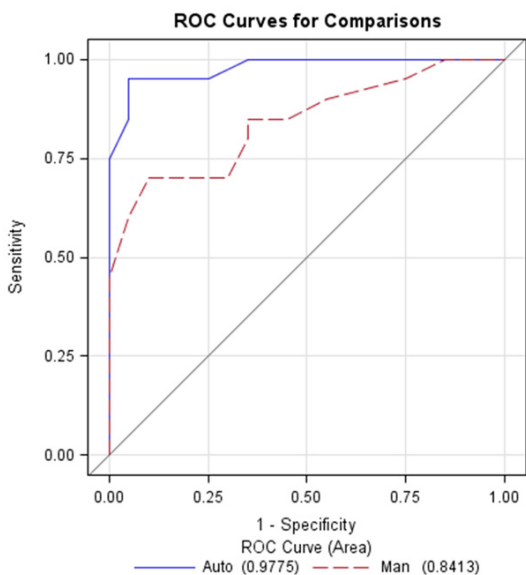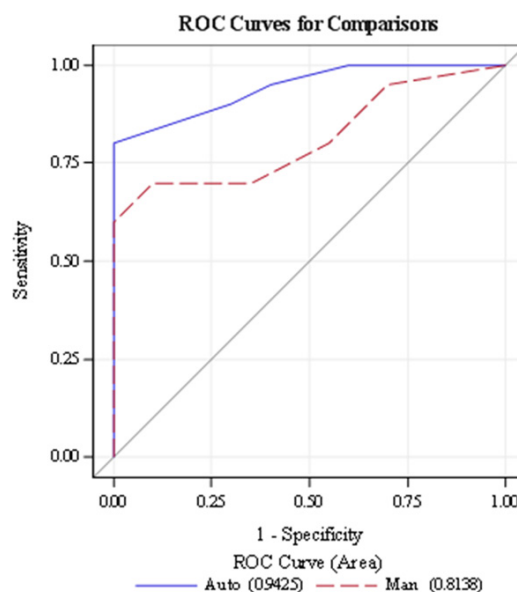

Figure 3. ROC curve using the average of all three readers along with the ROC associated statistics comparing software-aided vs. visual readings for normal vs. abnormal readings.

Figure 4. ROC curve using the average of all three readers along with the ROC associated statistics comparing software-aided vs. visual readings for absence vs. presence of Alzheimer's disease.

al approach. Furthermore, the AUC ROC increased with statistical significance comparing the software-aided approach versus the manual assessment for the detection of both, abnormality and AD.

The subject selection in our study focused on patients with mild or questionable AD in the early disease stage. We wanted to focus on this population subtype for two reasons: 1) early

diagnosis of AD is important as treatment is most effective during early stages of the disease [31] and 2) early stage AD is more challenging to diagnose compared to moderate to late stage AD [25].

Due to the increasing number of therapeutic options, the early and accurate diagnosis of AD is playing an increasingly important role [32,

18

33] as emphasized by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) [34, 35]. The current clinical climate stresses the importance of having an effective approach to diagnose AD non-invasively at early stages.

The clinical diagnosis of AD without the aid of imaging may be challenging. Depression, aphasia, and apraxia can mimic clinical criteria of AD [36, 37]. This coupled with the difficulty of distinguishing normal age related memory loss and rapid memory deterioration in early stage AD increases the complexity of AD diagnosis [38]. [18]F FDG PET imaging has made advances in enabling the diagnosis of AD in patients with confounding mental conditions [39] and has shown good accuracy in the discrimination of probable AD patients from normal subjects (95% sensitivity and 100% specificity using voxel-based z-scores and stereotactic surface projections) [21].

The addition of a software aided approach alongside qualitative visual interpretation could significantly improve the current clinical diagnostic performance of early stage AD.

The use of quantitation to improve the diagnosis of AD using FDG PET has been studied previously. One study demonstrated that 3D-SSP could improve reader diagnostic accuracy in subjects with AD compared to standard transaxial section presentation of the FDG PET scan [25]. The benefit of 3D-SSP was attributed to readers only being presented with the surface of the brain, allowing them to interpret less information. This study included subjects with moderate to severe dementia (CDR 2.0 and 3.0) in addition to those with milder dementia (CDR of 0.5 or 1.0) which were used in our study. In another study it was shown that using regional cerebral blood flow reduction in posterior cingulate gyri and precunei on voxel-based 3D-SSP as diagnostic criteria [21] produced a diagnostic accuracy of greater than 85% for patients with mild AD (CDR score of 0.5) and that 3D-SSP was a feasible tool for aiding to the visual diagnosis of AD [26]. Contrary to our study, the authors used SPECT rather than ^{18}F FDG PET. In a study looking at the effect of a voxel-based 3D-SSP approach for both beginners and experts over visual analysis alone it was found that that 3D-SSP significantly improved diagnostic specificity in both begin-

ners (0.26 to 0.63) and experienced readers (0.56 to 0.87) without a significant decrease in sensitivity (0.83 to 0.82) [40]. This minimal decrease in sensitivity from the voxel based 3D-SSP approach corresponded to the change in sensitivity from the software-aided approach in our study (0.72 to 0.73 P = 0.74). In addition, the use of voxel-based 3D-SSP significantly improved the interpretative confidence for all readers compared to the visual approach.

Fully automated quantitative software approaches without reader input have shown improvements in terms of AD diagnostic accuracy compared to beginner readers [41, 42]. However, a previous study has shown that an automatic diagnostic system relying solely on voxel based parametric mapping without reader input produced significantly lower AD diagnostic sensitivity compared to experienced readers [43]. Nevertheless, one benefit of a software-aided approach is its ability to improve reader specificity, especially for readers who may overemphasize physiological minimal changes that are part of inter-subject variability [43]. Our study has shown that voxel based quantitative adjunct software improves early AD diagnostic specificity and accuracy while maintaining similar sensitivity for experienced readers, emphasizing the importance of a software aided approach with final assessment by reading physicians as opposed to a fully automatic approach.

Our study has several limitations including the confounding effect of senile brain atrophy, which mimics glucose hypometabolism seen in AD [44]. The minimal amount of metabolic and perfusion changes seen in both mild stages of late-onset AD and senile dementia may influence interpretation of PET images, especially for elderly patients [45-47]. The training session provided to readers before PET interpretation was aimed to reduce the confounding effect of brain atrophy, a challenge encountered during study readouts. In addition, our study included a limited sample of subjects, as only 20 subjects with mild AD were included along with 20 normal control subjects. Hence, the direct scope of our results and conclusion was limited to patients that exhibit mild, borderline AD. Nevertheless, the changes in diagnostic specificity and accuracy were statistically

significant despite the small sample size. Despite this limitation, the statistically significant results suggest that our software aided approach would be successful in aiding diagnosis of both moderate and severe AD. As AD progresses in severity the physiologic manifestations and hallmark metabolic changes become more pronounced. We hypothesize that software aided evaluation would continue to demonstrate statistically significant increases in diagnostic capability, though as the physiologic derangements become more pronounced the magnitude of effect may decrease compared to the values we achieved with mild AD. Furthermore, the diagnosis of AD for the study subjects was determined by clinical criteria rather than the gold standard histopathology. This may impact the diagnostic accuracy of both approaches in the study, as the true presence of AD in each subject was not determined. However, the long clinical follow-up and imaging at 6, 12, and 24 months strengthened our assessment of the clinical diagnosis as well as positive amyloid scans for the AD subjects and negative amyloid scans for the controls. In addition, reader 1 (our most experienced reader) had a twenty percent increase in sensitivity of presence/absence of AD when switching from software-aided to manual approach. The accuracy, sensitivity, and specificity of reader 1 with quantitative software guidance for normal/abnormal reading were very high (0.875, 0.90, and 0.85, respectively). Hence, it may be that this increase in sensitivity of AD diagnosis was due to the reader attributing atrophy related changes seen on quantitative analysis to causes other than AD. Furthermore, our study utilized two parameters, normal/abnormal and presence of AD/absence of AD, to evaluate each ^{18}F FDG PET scan. This was done to address that the ADNI database has classified subjects based on clinical evaluation-which has been shown to potentially include subjects with glucose metabolism patterns more consistent with FTD or Lewy Body Dementia (LBD) as AD [48]. Although our subject selection criteria require a positive amyloid scan for mild AD subjects, LBD subjects may also present with a positive amyloid scan. Therefore, we used an additional parameter of normal vs. abnormal pattern of metabolism to include scans that indicate an abnormal pattern of metabolism without expressing a pattern consistent with AD. Finally, our study considered a score 3 on a 5 point scale to be indicative of an abnormal finding/presence of AD. This is an equivocal and subjective decision as it may also be interpreted as normal/absence of AD or an indeterminate outcome. However, scores of 3 out of 5 represented less than 10% of total reads and thus did not play a role in determining the results of our study.

For future studies, additional quantitative metrics could be used including region-based analysis to assess characteristic regional hypometabolism, which could further aid diagnostic performance. Furthermore, a comparison of diagnostic effectiveness of voxel SSP and voxel transaxial section quantitative approaches could further highlight the effect of 3D projections of the brain surface, as previously mentioned [25]. Finally, our study indicated that quantitative software-aided improved diagnostic accuracy of abnormality and AD in comparison to the manual approach. At the same time, it would be of interest to further investigate the potential diagnostic benefit of a dual-read approach that incorporates a preliminary manual read followed by a software-aided diagnosis.

Conclusion

The quantitative software-aided approach appears to improve the performance of ^{18}F FDG PET for the diagnosis of mild AD. The software-aided approach improves the diagnostic accuracy and specificity of mild AD while maintaining a similar level of sensitivity. Quantitative voxel based software may be helpful for experienced ^{18}F FDG PET readers analyzing early onset AD.

Acknowledgements

Disclosure of conflict of interest

This study was investigator initiated and supported by MIM Software Inc. Peter Faulhaber is consultant for MIM Software Inc. Peter Faulhaber is speaker for Philips Healthcare and has research grants from Philips Healthcare. Aaron Nelson has part ownership and is an employee of MIM Software Inc. Sara Pirozzi is an employee of MIM Software Inc.

Authors' contribution

*Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wpc-ontent/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

Address correspondence to: Peter Faulhaber, Department of Radiology, University Hospitals Cleveland Medical Center, Case Western Reserve University, 11100 Euclid Avenue, 44106, Cleveland, OH, USA. Tel: 216-844-8140; Fax: 216-844-3106; E-mail: peter.faulhaber@uhhospitals.org

References

[1]   Hebert LE, Beckett LA, Scherr PA and Evans DA. Annual incidence of Alzheimer disease in the United States projected to the years 2000 through 2050. Alzheimer Dis Assoc Disord 2001; 15: 169-173.

[2]   Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, Gamst A, Holtzman DM, Jagust WJ, Petersen RC, Snyder PJ, Carrillo MC, Thies B and Phelps CH. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National institute on Aging-Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011; 7: 270-279.

[3]   Lin JS, O'Connor E, Rossom RC, Perdue LA and Eckstrom E. Screening for cognitive impairment in older adults: a systematic review for the U.S. Preventive services task force. Ann Intern Med 2013; 159: 601-612.

[4]   Folstein MF, Folstein SE and McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189-198.

[5]   Mitchell AJ. A meta-analysis of the accuracy of the mini-mental state examination in the detection of dementia and mild cognitive impairment. J Psychiatr Res 2009; 43: 411-431.

[6]   Mungas D, Marshall SC, Weldon M, Haan M and Reed BR. Age and education correction of mini-mental state examination for english and Spanish-speaking elderly. Neurology 1996; 46: 700-706.

[7]   Brown RK, Bohnen NI, Wong KK, Minoshima S and Frey KA. Brain PET in suspected dementia: patterns of altered FDG metabolism. Radiographics 2014; 34: 684-701.

[8]   Mehta L and Thomas S. The role of PET in dementia diagnosis and treatment. Appl Radiol 2012; 41: 8.

[9]   Kershah S, Partovi S, Traughber BJ, Muzic RF Jr, Schluchter MD, O'Donnell JK and Faulhaber P. Comparison of standardized uptake values in normal structures between PET/CT and PET/MRI in an oncology patient population. Mol Imaging Biol 2013; 15: 776-785.

[10]   Shivamurthy VK, Tahari AK, Marcus C and Subramaniam RM. Brain FDG PET and the diagnosis of dementia. AJR Am J Roentgenol 2015; 204: W76-85.

[11]   McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC,

Thies B, Weintraub S and Phelps CH. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National institute on Aging-Alzheimer's association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011; 7: 263-269.

[12] Minoshima S, Foster NL and Kuhl DE. Posterior cingulate cortex in Alzheimer's disease. Lancet 1994; 344: 895.

[13] Herholz K. FDG PET and differential diagnosis of dementia. Alzheimer Dis Assoc Disord 1995; 9: 6-16.

[14] Hirono N, Mori E, Ishii K, Ikejiri Y, Imamura T, Shimomura T, Hashimoto M, Yamashita H and Sasaki M. Frontal lobe hypometabolism and depression in Alzheimer's disease. Neurol 1998; 50: 380-383.

[15] Oshima E, Terada S, Sato S, Ikeda C, Oda K, Inoue S, Kawada K, Yokota O and Uchitomi Y. Left frontal lobe hypoperfusion and depressive symptoms in Alzheimer's disease patients taking cholinesterase inhibitors. Psychiatry Res 2014; 224: 319-323.

[16] Minoshima S, Giordani B, Berent S, Frey KA, Foster NL and Kuhl DE. Metabolic reduction in the posterior cingulate cortex in very early Alzheimer's disease. Ann Neurol 1997; 42: 85-94.

[17] Silverman DH, Small GW, Chang CY, Lu CS, Kung De Aburto MA, Chen W, Czernin J, Rapoport SI, Pietrini P, Alexander GE, Schapiro MB, Jagust WJ, Hoffman JM, Welsh-Bohmer KA, Alavi A, Clark CM, Salmon E, de Leon MJ, Mielke R, Cummings JL, Kowell AP, Gambhir SS, Hoh CK and Phelps ME. Positron emission tomography in evaluation of dementia: regional brain metabolism and long-term outcome. JAMA 2001; 286: 2120-2127.

[18] Reiman EM, Chen K, Alexander GE, Caselli RJ, Bandy D, Osborne D, Saunders AM and Hardy J. Correlations between apolipoprotein E epsilon4 gene dose and brain-imaging measurements of regional hypometabolism. Proc Natl Acad Sci U S A 2005; 102: 8299-8302.

[19] Bloudek LM, Spackman DE, Blankenburg M and Sullivan SD. Review and meta-analysis of biomarkers and diagnostic imaging in Alzheimer's disease. J Alzheimers Dis 2011; 26: 627-645.

[20] Mosconi L, Tsui WH, Herholz K, Pupi A, Drzezga A, Lucignani G, Reiman EM, Holthoff V, Kalbe E, Sorbi S, Diehl-Schmid J, Perneczky R, Clerici F, Caselli R, Beuthien-Baumann B, Kurz A, Minoshima S and de Leon MJ. Multicenter standardized ^{18}F-FDG PET diagnosis of mild cognitive impairment, Alzheimer's disease, and other dementias. J Nucl Med 2008; 49: 390-398.

[21] Minoshima S, Frey KA, Koeppe RA, Foster NL and Kuhl DE. A diagnostic approach in Alzheimer's disease using three-dimensional stereotactic surface projections of fluorine-18-FDG PET. J Nucl Med 1995; 36: 1238-1248.

[22] Signorini M, Paulesu E, Friston K, Perani D, Colleluori A, Lucignani G, Grassi F, Bettinardi V, Frackowiak R and Fazio F. Rapid assessment of regional cerebral metabolic abnormalities in single subjects with quantitative and nonquantitative [^{18}F] FDG PET: a clinical validation of statistical parametric mapping. Neuroimage 1999; 9: 63-80.

[23] Herholz K, Salmon E, Perani D, Baron JC, Holthoff V, Frolich L, Schonknecht P, Ito K, Mielke R, Kalbe E, Zundorf G, Delbeuck X, Pelati O, Anchisi D, Fazio F, Kerrouche N, Desgranges B, Eustache F, Beuthien-Baumann B, Menzel C, Schroder J, Kato T, Arahata Y, Henze M and Heiss WD. Discrimination between Alzheimer dementia and controls by automated analysis of multicenter FDG PET. Neuroimage 2002; 17: 302-316.

[24] Jagust WJ, Bandy D, Chen K, Foster NL, Landau SM, Mathis CA, Price JC, Reiman EM, Skovronsky D, Koeppe RA; Alzheimer's Disease Neuroimaging Initiative. The Alzheimer's disease neuroimaging initiative positron emission tomography core. Alzheimers Dement 2010; 6: 221-229.

[25] Burdette JH, Minoshima S, Vander Borght T, Tran DD and Kuhl DE. Alzheimer disease: improved visual interpretation of PET images by using three-dimensional stereotaxic surface projections. Radiology 1996; 198: 837-843.

[26] Imabayashi E, Matsuda H, Asada T, Ohnishi T, Sakamoto S, Nakano S and Inoue T. Superiority of 3-dimensional stereotactic surface projection analysis over visual inspection in discrimination of patients with very early Alzheimer's disease from controls using brain perfusion SPECT. J Nucl Med 2004; 45: 1450-1457.

[27] Kuhl D. Imaging local brain function with emission computed tomography. Radiology 1984; 150: 625-631.

[28] Foster NL, Chase TN, Mansi L, Brooks R, Fedio P, Patronas NJ and Di Chiro G. Cortical abnormalities in Alzheimer's disease. Ann Neurol 1984; 16: 649-654.

[29] Mielke R, Schröder R, Fink G, Kessler J, Herholz K and Heiss WD. Regional cerebral glucose metabolism and postmortem pathology in Alzheimer's disease. Acta Neuropathol 1996; 91: 174-179.

[30] Womack KB, Diaz-Arrastia R, Aizenstein HJ, Arnold SE, Barbas NR, Boeve BF, Clark CM, DeCarli CS, Jagust WJ and Leverenz JB. Temporo-

parietal hypometabolism in frontotemporal lobar degeneration and associated imaging diagnostic errors. Arch Neurol 2011; 68: 329-337.

[31] Duara R, Barker W, Loewenstein D and Bain L. The basis for disease-modifying treatments for Alzheimer's disease: the sixth annual mild cognitive impairment symposium. Alzheimers Dement 2009; 5: 66-74.

[32] Schenk D. Amyloid-β immunotherapy for Alzheimer's disease: the end of the beginning. Nat Rev Neurosci 2002; 3: 824-828.

[33] Citron M. Strategies for disease modification in Alzheimer's disease. Nat Rev Neurosci 2004; 5: 677-685.

[34] Jack CR, Albert MS, Knopman DS, McKhann GM, Sperling RA, Carrillo MC, Thies B and Phelps CH. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011; 7: 257-262.

[35] Dubois B, Feldman HH, Jacova C, Hampel H, Molinuevo JL, Blennow K, DeKosky ST, Gauthier S, Selkoe D and Bateman R. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol 2014; 13: 614-629.

[36] Kramer JH, Miller BL. Alzheimer's disease and its focal variants. Semin Neurol 2000; 20: 447-54.

[37] Cummings JL. Cognitive and behavioral heterogeneity in Alzheimer's disease: seeking the neurobiological basis. Neurobiol Aging 2000; 21: 845-861.

[38] Norfray JF and Provenzale JM. Alzheimer's disease: neuropathologic findings and recent advances in imaging. AJR Am J Roentgenol 2004; 182: 3-13.

[39] Hoffman JM, Welsh-Bohmer KA, Hanson M, Crain B, Hulette C, Earl N and Coleman RE. FDG PET imaging in patients with pathologically verified dementia. J Nucl Med 2000; 41: 1920-1928.

[40] Lehman VT, Carter RE, Claassen DO, Murphy RC, Lowe V, Petersen RC and Peller PJ. Visual assessment versus quantitative three-dimensional stereotactic surface projection fluorodeoxyglucose positron emission tomography for detection of mild cognitive impairment and Alzheimer disease. Clin Nucl Med 2012; 37: 721-726.

[41] Kono AK, Ishii K, Sofue K, Miyamoto N, Sakamoto S and Mori E. Fully automatic differential diagnosis system for dementia with Lewy bodies and Alzheimer's disease using FDG-PET and 3D-SSP. Eur J Nuc Med Mol 2007; 34: 1490-1497.

[42] Ishii K, Kono AK, Sasaki H, Miyamoto N, Fukuda T, Sakamoto S and Mori E. Fully automatic diagnostic system for early-and late-onset mild Alzheimer's disease using FDG PET and 3D-SSP. Eur J Nucl Med Mol Imaging 2006; 33: 575-583.

[43] Morbelli S, Brugnolo A, Bossert I, Buschiazzo A, Frisoni GB, Galluzzi S, van Berckel BN, Ossenkoppele R, Perneczky R, Drzezga A, Didic M, Guedj E, Sambuceti G, Bottoni G, Arnaldi D, Picco A, De Carli F, Pagani M and Nobili F. Visual versus semi-quantitative analysis of ^{18}F-FDG-PET in amnestic MCI: an European Alzheimer's disease consortium (EADC) project. J Alzheimers Dis 2015; 44: 815-826.

[44] Rodriguez-Oroz MC, Gago B, Clavero P, Delgado-Alvarado M, Garcia-Garcia D and Jimenez-Urbieta H. The relationship between atrophy and hypometabolism: is it regionally dependent in dementias? Curr Neurol Neurosci Rep 2015; 15: 1-12.

[45] Mielke R, Herholz K, Grond M, Kessler J and Heiss WD. Differences of regional cerebral glucose metabolism between presenile and senile dementia of Alzheimer type. Neurobiol Aging 1992; 13: 93-98.

[46] Sakamoto S, Ishii K, Sasaki M, Hosaka K, Mori T, Matsui M, Hirono N and Mori E. Differences in cerebral metabolic impairment between early and late onset types of Alzheimer's disease. J Neurol Sci 2002; 200: 27-32.

[47] Ng S, Villemagne VL, Berlangieri S, Lee ST, Cherk M, Gong SJ, Ackermann U, Saunder T, Tochon-Danguy H and Jones G. Visual assessment versus quantitative assessment of 11C-PIB PET and ^{18}F-FDG PET for detection of Alzheimer's disease. J Nuc Med 2007; 48: 547-552.

[48] Gray K, Wolz R, Heckemann RA, et al. Multi-region analysis of longitudinal FDG-PET for the classification of AD. Neuroimage 2012; 60: 221-229.