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**Molecular imaging in the diagnosis of Alzheimer's disease:
visual assessment of [¹¹C]PIB and [¹⁸F]FDDNP PET images**

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Abstract

Objective: To evaluate visual assessment of [^{11}C]PIB and [^{18}F]FDDNP PET images as potential supportive diagnostic markers for Alzheimer's disease (AD).

Methods: Twenty-one AD patients and 20 controls were included. Parametric [^{11}C]PIB and [^{18}F]FDDNP BP_{ND} images were visually rated as 'AD' or 'normal'. Data were compared with ratings of [^{18}F]FDG PET images and MRI derived medial temporal lobe atrophy (MTA) scores. Inter-rater agreement and agreement with clinical diagnosis was assessed for all imaging modalities. In addition, cut-off values for quantitative global [^{11}C]PIB and [^{18}F]FDDNP BP_{ND} were determined. Visual ratings were compared with dichotomised quantitative values.

Results: Agreement between readers was excellent for [^{11}C]PIB, [^{18}F]FDDNP and MTA (Cohen's kappa $\kappa \geq 0.85$) and moderate for [^{18}F]FDG ($\kappa = 0.56$). Highest sensitivity was found for [^{11}C]PIB and [^{18}F]FDG (both 1.0). Highest specificity was found for MTA (0.90) and [^{11}C]PIB (0.85). [^{18}F]FDDNP had lowest sensitivity and specificity (0.67 and 0.53, respectively). Cut-off for quantitative [^{11}C]PIB BP_{ND} was 0.54 (sensitivity and specificity both 0.95) and for [^{18}F]FDDNP BP_{ND} 0.07 (sensitivity 0.80, specificity 0.73). Agreement between quantitative analyses and visual ratings was excellent for [^{11}C]PIB ($\kappa = 0.85$) and fair for [^{18}F]FDDNP ($\kappa = 0.40$).

Conclusion: Visual assessment of [^{11}C]PIB images was straightforward and accurate, showing promise as a supportive diagnostic marker for AD. Moreover, [^{11}C]PIB showed the best combination of sensitivity and specificity. Visual assessment of [^{18}F]FDDNP images was insufficient. Quantitative analysis of [^{18}F]FDDNP data showed considerable higher diagnostic value than visual analysis.

Introduction

Recently, several PET tracers have been developed for visualising AD pathology directly. Of these ligands, [^{11}C]PIB (Pittsburgh Compound-B)¹ and [^{18}F]FDDNP (2-(1-{6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-aphthyl} ethylidene) malononitrile)² have been used most widely. Both tracers have shown the ability to distinguish AD patients from controls at a group level.¹⁻⁴ However, little is known about accuracy and reliability of visual assessment of images acquired using these new biomarkers. The aim of the present study was to compare visual assessment of [^{11}C]PIB and [^{18}F]FDDNP images as potential supportive diagnostic markers for AD. Results were compared with those of visual assessment of decreased cerebral glucose metabolism [^{18}F]FDG and with medial temporal lobe atrophy (MTA) using magnetic resonance imaging (MRI)⁵. In addition, visual assessment of [^{11}C]PIB and [^{18}F]FDDNP images was compared with quantitative assessment of global binding.

Methods

Subjects

Twenty-one AD patients (mean±SD 63±6 years) and 20 controls (67±6 years) were included in this study. Global and regional [^{11}C]PIB and [^{18}F]FDDNP binding in a largely overlapping sample have been reported elsewhere.⁴ [^{11}C]PIB and MRI scans were available for all subjects. [^{18}F]FDDNP PET scans were not available for 5 AD patients and 5 controls and [^{18}F]FDG scans were not available for 5 controls.

Assessment protocol and PET and MRI scanning protocols have been described previously⁴ and can be found as supplementary material online.

Visual readings

All scans were presented to the readers in a randomised order. All [^{11}C]PIB, [^{18}F]FDDNP and [^{18}F]FDG scans were rated separately by 2 readers (BvB and PR for [^{11}C]PIB and [^{18}F]FDDNP; BvB and KH for [^{18}F]FDG) and classified as either AD or normal (i.e. unlikely to be AD). For rating of [^{18}F]FDG, readers had access to results of the Alzheimer discrimination tool,⁶ but the final decision was based on their own assessment. Readers of PET scans were nuclear medicine physicians (BB, PR) and a neurologist (KH) with expertise in PET imaging and they were blinded to clinical information. Results of individual readers were compared and discrepancies were discussed to establish consensus.

Atrophy rating on T1 weighted MRI was separately performed by 2 trained neuroradiologists (FB and MW), who were blinded to clinical information, but had knowledge of the age of the subject. MTA was rated visually on the oblique/coronal images using a scale ranging from 0 (no atrophy) to 4 (severe atrophy))⁵ Averaged MTA scores were dichotomised according to age. MTA scores were considered as abnormal depending on age (years), i.e. ≥ 1 for subjects

<65, ≥ 1.5 for subjects ≥ 65 and < 75, and ≥ 2 for subjects ≥ 75 years. MTA ratings of the most experienced reader (FB) were used for further analysis, as consensus was not available.

Statistical analysis

Data are presented as mean $\pm$ SD, unless otherwise stated. Frequency distributions for gender were compared using the Chi-square test. Differences between the two groups were assessed using analysis of variance (ANOVA) with age and gender as covariates.

To assess consistency of visual assessments, Cohen's Kappa (κ)⁷ for agreement between readers was calculated for all imaging modalities. Sensitivity, specificity, likelihood ratios and accuracy were calculated for visual assessment of [¹¹C]PIB, [¹⁸F]FDDNP and [¹⁸F]FDG images, and for MTA. Clinical diagnosis was used as reference criterion.

Next, agreement between visual assessment of [¹¹C]PIB and [¹⁸F]FDDNP images and corresponding quantitative values of global binding potential (BP_{ND}) was assessed. To this end, receiver-operating-characteristic (ROC) curves were generated to determine optimal cut-off values for global [¹¹C]PIB and [¹⁸F]FDDNP BP_{ND}. Optimal cut-off values were defined as those values that yielded at least 80% sensitivity, with accompanying specificity for detecting AD,⁸ using clinical diagnosis as reference criterion. Based on these ROC defined cut-off values, quantitative BP_{ND} values of all subjects were classified as 'normal' or 'abnormal' and agreement between quantitative and visual assessments was assessed using Cohen's Kappa.

Results

Demographic and clinical characteristics according to diagnostic group, together with examples of normal and AD-like images for all modalities, are provided as supplementary material online (Table A and Figure A).

Agreement between readers

Agreement between visual readings was excellent for [^{11}C]PIB ($\kappa=0.85$), [^{18}F]FDDNP ($\kappa=0.87$) and MTA ($\kappa=0.90$), and moderate for [^{18}F]FDG ($\kappa=0.56$).

Agreement with clinical diagnosis

Sensitivity, specificity, LR+, LR- and accuracy for visual assessment of all imaging modalities are presented in Table 1. [^{11}C]PIB and [^{18}F]FDG had the highest sensitivity (all patients were identified correctly). Lowest sensitivity was obtained for [^{18}F]FDDNP and MTA. Highest specificity was found for MTA and [^{11}C]PIB. [^{18}F]FDG and [^{18}F]FDDNP had low specificity. Sensitivity and specificity were reflected in LR as highest LR+ for MTA and best LR- for both [^{11}C]PIB and [^{18}F]FDG. Highest accuracy was found for [^{11}C]PIB, whilst it was lowest for [^{18}F]FDDNP. MTA and [^{18}F]FDG has similar accuracy.

Agreement with quantitative analysis

ROC curves were generated to determine optimal cut-off values for both ligands (for ROC curves, see supplementary material online, Figure B). The [^{11}C]PIB cut-off value was determined at a BP_{ND} of 0.54. The area under the curve (AUC) was 0.96 (95% confidence interval (CI) 0.90-1.03), with both sensitivity and specificity of 0.95. These values differed only slightly from sensitivity and specificity of visual ratings. For global [^{18}F]FDDNP binding the optimal cut-off value was found to be at a BP_{ND} of 0.07, resulting in a sensitivity of 0.80,

a specificity of 0.73 and an AUC (95% CI) of 0.85 (0.71-0.99), which were considerably higher than corresponding values found with visual ratings.

Agreement of quantitative assessment between both ligands is illustrated in Figure 1, where the reference lines indicate cut-off values of both tracers. Agreement between quantitative analysis and visual rating was excellent for [^{11}C]PIB ($\kappa=0.85$) and fair for [^{18}F]FDDNP ($\kappa=0.40$).

Discussion

This study evaluated visual assessment of [^{11}C]PIB and [^{18}F]FDDNP images as potential supportive diagnostic markers for AD. Visual assessment of [^{11}C]PIB images showed a high diagnostic accuracy combined with high inter-observer agreement. Furthermore, agreement between visual and quantitative assessment of [^{11}C]PIB was high. Moreover, in the present cohort, visual rating of [^{11}C]PIB for identification of AD performed equally well as the combination of [^{18}F]FDG (high sensitivity) and MTA (high specificity). Diagnostic accuracy of [^{11}C]PIB was even higher than that of other markers. Visual rating of [^{18}F]FDDNP images for identification of AD had the lowest sensitivity, specificity and accuracy. Additionally, agreement with quantitative assessment was only fair.

The findings are in line with a previously published study⁹ evaluating visual assessment of [^{11}C]PIB and [^{18}F]FDG, reporting similar agreement between readers for both modalities and similar sensitivity and specificity for [^{11}C]PIB.

The low accuracy of visual assessment of [^{18}F]FDDNP may be due to the fact that the difference in [^{18}F]FDDNP BP_{ND} between AD patients and controls is subtle,²⁻⁴ therefore hampering visual assessment. Quantitative assessment of [^{18}F]FDDNP scans was considerably better in identifying AD and could therefore still be a potential tool in diagnosing dementia. This is especially true as [^{18}F]FDDNP is the only PET ligand available to date, which also has affinity for tangle pathology.¹⁰

Post mortem studies report presence of AD pathology in around 30% of cognitively healthy elderly subjects¹¹ and other imaging studies report increased [^{11}C]PIB uptake in around 30% cognitively normal elderly subjects.¹²⁻¹⁴ Visual assessment of [^{11}C]PIB images in the present study rated three out of twenty cognitively healthy elderly subjects as abnormal. This relatively low percentage, however, is likely to be due to the relatively young age of subjects in the present study.

These control subjects with abnormal [^{11}C]PIB images may be preclinical AD patients, as deposition of pathology is thought to start a decade before cognitive impairment arises.¹⁵ Alternatively, deposition of amyloid could have a more benign character, not leading to clinical AD. To verify whether these subjects are indeed preclinical cases will require longitudinal follow up studies. Assuming that these subjects are indeed preclinical rather than false positive cases, specificity for the other imaging modalities would likely to also have been affected, resulting in falsely low specificity estimates.¹⁶

A limitation of the study is that readings of imaging modalities were dichotomised. Especially [^{18}F]FDG provides a graded answer and forcing it into just two alternatives does not lead to use of its full potential. Therefore the diagnostic accuracy of [^{18}F]FDG in the present study might be lower than the diagnostic value in clinical practice.

The present study contributes to the discussion on new supportive biomarkers for diagnosing AD¹⁷ as it provides a comparison of the relative sensitivity and specificity of [^{11}C]PIB, [^{18}F]FDDNP, [^{18}F]FDG and MTA for visual classification of scans as AD or normal when readers are blind to clinical diagnosis. It should be kept in mind, however, that the values found for sensitivity, specificity, likelihood ratio's and accuracy are only an estimation of performance, as they are affected by both size and composition of the study sample. Nevertheless, as all imaging modalities were compared using the same sample, this should still provide a fair assessment of their relative specificity.

Table 1: Sensitivity, specificity, likelihood ratios and accuracy for visual ratings across AD patients and controls.

Visual rating	Sensitivity	Specificity	LR+	LR-	Accuracy
[¹¹ C]PIB	1.0 (21/21)	0.85 (17/20)	6.7	0	0.93
[¹⁸ F]FDDNP	0.67 (10/15)	0.53 (8/15)	1.5	0.6	0.60
[¹⁸ F]FDG	1.00 (21/21)	0.56 (9/16)	2.3	0	0.81
MTA	0.71 (15/21)	0.90 (18/20)	7.1	0.3	0.80

MTA; medial temporal lobe atrophy, LR+; positive likelihood ratio, LR-; negative likelihood ratio

Numbers between brackets represent numbers of patients

If sensitivity =1, LR- =0, if specificity=1, LR+ =0

Figure legend

Figure 1: Agreement between quantitative assessment of global [^{11}C]PIB and [^{18}F]FDDNP BP_{ND} with [^{18}F]FDDNP binding on the x-axis and [^{11}C]PIB binding on the y-axis. Reference lines represent cut-off values. The right upper quadrant contains subjects with relatively high binding for both ligands, whilst the left lower quadrant displays subjects with relatively low binding for both ligands. AD patients are represented by circles and controls by squares. For [^{11}C]PIB, all AD patients showed high global BP_{ND} , whilst only one control subject showed binding above the cut-off value. For [^{18}F]FDDNP, 3 AD patients showed global binding below and 4 controls global binding above the cut-off value.

Reference List

1. **Klunk WE**, Engler H, Nordberg A, Wang Y, Blomqvist G, Holt DP, Bergstrom M, Savitcheva I, Huang GF, Estrada S, Ausen B, Debnath ML, Barletta J, Price JC, Sandell J, Lopresti BJ, Wall A, Koivisto P, Antoni G, Mathis CA, Langstrom B. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Ann.Neurol.* 2004;**55**:306-19.
2. **Small GW**, Kepe V, Ercoli LM, Siddarth P, Bookheimer SY, Miller KJ, Lavretsky H, Burggren AC, Cole GM, Vinters HV, Thompson PM, Huang SC, Satyamurthy N, Phelps ME, Barrio JR. PET of brain amyloid and tau in mild cognitive impairment. *N.Engl.J.Med.* 2006;**355**:2652-63.
3. **Shin J**, Lee SY, Kim SH, Kim YB, Cho SJ. Multitracer PET imaging of amyloid plaques and neurofibrillary tangles in Alzheimer's disease. *Neuroimage* 2008;236-344.
4. **Tolboom N**, Yaqub M, van der Flier WM, Boellaard R, Luurtsema G, Windhorst AD, Barkhof F, Scheltens P, Lammertsma AA, van Berckel BN. Detection of Alzheimer Pathology In Vivo Using Both 11C-PIB and 18F-FDDNP PET. *J Nucl.Med.* 2009;**50**:191-7.
5. **Scheltens P**, Leys D, Barkhof F, Huglo D, Weinstein HC, Vermersch P, Kuiper M, Steinling M, Wolters EC, Valk J. Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. *J Neurol.Neurosurg.Psychiatry* 1992;**55**:967-72.
6. **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, Heiss WD. Discrimination between Alzheimer dementia and controls by automated analysis of multicenter FDG PET. *Neuroimage* 2002;**17**:302-16.

7. **Landis JR**, Koch GG. An application of hierarchical kappa-type statistics in the assessment of majority agreement among multiple observers. *Biometrics* 1977;**33**:363-74.
8. Consensus report of the Working Group on: "Molecular and Biochemical Markers of Alzheimer's Disease". The Ronald and Nancy Reagan Research Institute of the Alzheimer's Association and the National Institute on Aging Working Group. *Neurobiol.Aging* 1998;**19**:109-16.
9. **Ng S**, Villemagne VL, Berlangieri S, Lee ST, Cherk M, Gong SJ, Ackermann U, Saunderson T, Tochon-Danguy H, Jones G, Smith C, O'Keefe G, Masters CL, Rowe CC. Visual assessment versus quantitative assessment of 11C-PIB PET and 18F-FDG PET for detection of Alzheimer's disease. *J.Nucl.Med.* 2007;**48**:547-52.
10. **Agdeppa ED**, Kepe V, Liu J, Flores-Torres S, Satyamurthy N, Petric A, Cole GM, Small GW, Huang SC, Barrio JR. Binding characteristics of radiofluorinated 6-dialkylamino-2-naphthylethylidene derivatives as positron emission tomography imaging probes for beta-amyloid plaques in Alzheimer's disease. *J.Neurosci.* 2001;**21**:RC189.
11. **Price JL**, Morris JC. Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. *Ann.Neurol.* 1999;**45**:358-68.
12. **Aizenstein HJ**, Nebes RD, Saxton JA, Price JC, Mathis CA, Tsopelas ND, Ziolkowski SK, James JA, Snitz BE, Houck PR, Bi W, Cohen AD, Lopresti BJ, DeKosky ST, Halligan

EM, Klunk WE. Frequent amyloid deposition without significant cognitive impairment among the elderly. *Arch.Neurol.* 2008;**65**:1509-17.

13. **Pike KE**, Savage G, Villemagne VL, Ng S, Moss SA, Maruff P, Mathis CA, Klunk WE, Masters CL, Rowe CC. Beta-amyloid imaging and memory in non-demented individuals: evidence for preclinical Alzheimer's disease. *Brain* 2007;**130**:2837-44.
14. **Mintun MA**, LaRossa GN, Sheline YI, Dence CS, Lee SY, Mach RH, Klunk WE, Mathis CA, DeKosky ST, Morris JC. [11C]PIB in a nondemented population: potential antecedent marker of Alzheimer disease. *Neurology* 2006;**67**:446-52.
15. **Morris JC**, Price AL. Pathologic correlates of nondemented aging, mild cognitive impairment, and early-stage Alzheimer's disease. *J Mol.Neurosci.* 2001;**17**:101-18.
16. **Mosconi L**, Tsui WH, Pupi A, de SS, Drzezga A, Minoshima S, de Leon MJ. (18)F-FDG PET database of longitudinally confirmed healthy elderly individuals improves detection of mild cognitive impairment and Alzheimer's disease. *J Nucl.Med.* 2007;**48**:1129-34.
17. **Dubois B**, Feldman HH, Jacova C, DeKosky ST, Barberger-Gateau P, Cummings J, Delacourte A, Galasko D, Gauthier S, Jicha G, Meguro K, O'brien J, Pasquier F, Robert P, Rossor M, Salloway S, Stern Y, Visser PJ, Scheltens P. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurol.* 2007;**6**:734-46.