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The use of PIB-PET as a dual pathological and functional biomarker in AD ☆

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ABSTRACT

Amyloid imaging with positron emission tomography (PET) is presently used in Alzheimer's disease (AD) research. In this study we investigated the possibility to use early frames (ePIB) of the PIB scans as a rough index of CBF by comparing normalised early PIB values with cerebral glucose metabolism (rCMRglc). PIB-PET and FDG-PET were performed in 37 AD patients, 21 subjects with mild cognitive impairment (MCI) and 6 healthy controls (HC). The patients were divided based on their PIB retention (amyloid load) as either PIB positive (PIB+) or PIB negative (PIB−). Data of the unidirectional influx K_1 from a subset of the subjects including 7 AD patients and 3 HC was used for correlative analysis. Data was analysed using regions of interest (ROI) analysis. A strong, positive correlation was observed across brain regions between K_1 and ePIB ($r = 0.70$; $p \leq 0.001$). The ePIB values were significantly lower in the posterior cingulate ($p \leq 0.001$) and the parietal cortices ($p = 0.002$) in PIB+ subjects compared to PIB−, although the group difference were stronger for rCMRglc in cortical areas ($p \leq 0.001$). Strong positive correlations between ePIB and rCMRglc were observed in all cortical regions analysed, especially in the posterior cingulate and parietal cortices ($p \leq 0.001$). A single dynamic PIB-PET scan may provide information about pathological and functional changes (amyloidosis and impaired blood flow). This might be important for diagnosis of AD, enrichment of patients in clinical trials and evaluation of treatment effects. This article is part of a Special Issue entitled: Imaging Brain Aging and Neurodegenerative disease.

1. Introduction

PET imaging with amyloid tracers such as [^{11}C] *N*-methyl [^{11}C] 2-(4′methylaminophenyl)-6-hydroxy-benzothiazole (PIB) allows measurement of high cerebral amyloid-ß deposition in AD and thereby discriminating AD patients from healthy controls [1,2]. High amyloid-ß load has also been demonstrated by PIB in patients with mild cognitive impairment (MCI) that later converts to AD [3,2]. It has also been shown that PIB-PET may differentiate AD patients from patients with frontotemporal lobe dementia [4–6] or Parkinson's disease [4,7,8] whilst patients with dementia with Lewy bodies may show high but variable PIB retention [4,8,9]. Recently several amyloid tracers labelled with ^{18}F such as florbetaben,florbetapir and flutemetamol have been developed suitable for clinical PET facilities [2,10].

PET imaging of cerebral metabolic rate of glucose (CMRglc) using 2-[^{18}F]-2-deoxy-D-glucose (FDG) has been used to detect functional changes in AD with reduced FDG uptake especially in the temporal, parietal and posterior cingulate cortices [11,12]. Similar results have been obtained in studies of changes in cerebral blood flow (CBF) in AD patients [13–16]. Although both CMRglc and CBF have been suggested to be able to predict conversion from MCI to AD, FDG-PET seems to be somewhat superior [17,18]. One study however directly compared the diagnostic accuracy of CMRglc measured with FDG-PET and CBF measured by IMP-SPECT and observed no significant difference between the two measurements in diagnostic accuracy, and the two measurements correlated significantly in the parietotemporal cortex and posterior cingulate cortex/precuneus [16]. This result suggests that the two functional estimates, rCMRglc and CBF, are related

Abbreviations: PET, Positron emission tomography; AD, Alzheimer's disease; CBF, cerebral blood flow; FDG, [^{18}F]-2-deoxy-d-glucose; MCI, Mild cognitive impairments; HC, Healthy controls; MMSE, Mini-Mental State Examination; PIB, *N*-methyl [^{11}C] 2-(4′-methylaminophenyl)-6-hydroxy-benzothiazole; rCMRglc, regional cerebral metabolic rate of glucose; ROIs, regions of interest.

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and this comprised the background to evaluate the early frames of PIB imaging as a functional measurement of CBF.

The possibility to combine pathological and functional measurements would improve the accuracy in AD diagnostics and increase our understanding of neurodegenerative processes occurring in the brain of AD patients. Although it is possible to perform PIB- and FDG-PET scans in a patient at the same day [1] this procedure is time consuming, expensive, and demanding on the patient. It would be an advantage for clinical as well as research purposes to obtain, from a single PET scan, both pathological and functional measurements.

In an earlier study we combined data from rate constant K_1 for unidirectional influx across the brain barrier with data for PIB retention. We demonstrated dynamic PIB-PET data by using a kinetic model, with one reversible and one irreversible tissue compartment and three rate constants, to investigate the PIB net accumulation (K_{acc}) and unidirectional influx (K_1) across the blood brain barrier (BBB) in HC and AD patients [19]. We compared the results with the ratio between the retention in a target and reference region in a late interval (PIB), in HC and AD patients from previous studies [1]. The parameter K_{acc} and the PIB were found to have similar regional distributions. The rate constant K_1 for PIB was found to be comparatively large, demonstrating high extraction of PIB into brain and indicating that this time interval following tracer administration might reflect CBF [19]. We further showed in a controlled PET study of a rhesus monkey that K_1 correlated well with CBF measured with [^{15}O]H_2O which is the golden standard measurement of CBF, suggesting that unidirectional influx rate constant K_1 of PIB as a good index of CBF [19]. The aim of the present study was to investigate the possibility to replace K_1 by a simplified index of PIB uptake in the early time interval after tracer administration. Data from the early frames of the dynamic PIB (ePIB) was compared with K_1 and rCMRglc data in a set of AD patients, MCI patients and age matched healthy controls.

2. Material and methods

2.1. Subjects

PET data was obtained from 37 AD patients, 21 MCI patients and 6 healthy controls (HCs). The demographic data of the patients is shown in Table 1. All patients were recruited from the Department of Geriatric Medicine, Karolinska University Hospital Huddinge, Stockholm, Sweden. All AD and MCI patients had undergone a comprehensive assessment of memory problems including physical examination, evaluation of neurological and psychiatric status, blood analysis including apolipoprotein E (ApoE) genotyping, electroencephalography, magnetic resonance imaging, and/or single photon computed tomography (SPECT), cerebrospinal fluid analysis, and cognitive and neuropsychological testing.

The AD patients were diagnosed as probable AD according to the criteria of the National Institute of Neurological and Communication Disorders, Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [20]. None of the HCs had a history of a medical or neurological disease or substance abuse, and all scored normally on neuropsychological testing. The diagnosis of MCI was based upon the modified Petersen criteria [21,22]. All included subjects gave written consent to participate in the study. The Ethics Committees of Uppsala University, the Karolinska Institute and the Isotope Committee at Uppsala Academic Hospital approved the study.

A subset of data was used from the patients mentioned above, in which arterial sampling and kinetic modelling was performed, comprising of 7 AD patients with a mean age of 66 ± 10, and 3 healthy controls with a mean age of 57 ± 31 (21, 72 and 77 years old).

PIB-PET and FDG-PET data from the AD patients, MCI patients and HC have been used in previous publications [1,3,23]

Table 1
Demographic data of patients with Alzheimer's disease (AD), mild cognitive impairment (MCI) and healthy controls (HC).

	AD	MCI	HC
Age	67.5 ± 9.2	63.3 ± 7.8	69.0 ± 7.2
Gender (male/female)	17/20	8/13	3/3
MMSE	23.7 ± 4.0***	28.2 ± 1.4	30 ± 0
ApoE-ε4 carriers	25	14	–
PIB+/PIB−	32/5	11/10	1/5

*** $p<0.001$ (AD vs MCI).

2.2. PET scanning and data analysis

The subjects underwent PET examinations with PIB and FDG at Uppsala PET center, Uppsala, Sweden. Production of FDG and PIB was carried out according to good manufacturing standards at Uppsala PET center, and the synthesis of PIB was performed as previously described [1,24]. The tracer doses of PIB and FDG, and the scanner protocol for transmissions, emissions and reconstructions, as well as image pre-processing have previously been published [1,3].

Quantitative data of PIB retention and cerebral glucose metabolism (CMRglc) were generated as described in detail in previous studies [3,23]. Data from the early frames of the PIB (ePIB) were generated by summation of the frames from the first 6 min. Standard uptake values (SUV) were calculated and the data from the early frames (6 min) was normalised to the reference region in the cerebellar cortex using data from the same time interval (first 6 min). To account for global differences between patients the CMRglc data was normalised to the pons, a region with quite stable glucose metabolism during disease progression [25]. Modelling of the data rendering the K_1 parameter has been described in detail elsewhere [19].

The set of regions of interest (ROIs) used in statistical analysis has previously been described in detail [1,26]. Data from the frontal, parietal, temporal and primary visual cortices, posterior cingulate cortex, striatum, thalamus and white matter were included in the statistical analysis comparing patient groups. For correlative analysis across regions between K_1 and ePIB the same set of ROIs were used with some exceptions: posterior cingulate cortex was not included and a ROI at the level of thalamus including the whole brain was included.

Based on the PIB retention level two groups were created, one with high PIB retention (PIB+) and one with low PIB retention (PIB−). The cut-off level used was calculated as the mean plus one standard deviation above the level of the healthy controls and has been described before [3]. The cut-off level was calculated to 1.6, a number that is corresponding to what have been described in other PIB-PET studies [27–29]. The numbers of PIB+ and PIB− patients are shown in Table 1.

Analyses of group differences were conducted by using two-tailed Student's *t*-tests. Correlation analyses were conducted, using Pearson's product moment correlation coefficient r. No correction for multiple comparisons was done due to the explorative nature of this pilot study.

3. Results

3.1. Group differences in clinical parameters

The demographical and clinical parameters are described in Table 1. The AD patients showed a significant lower MMSE score compared to MCI patients. For further analysis the subjects were divided in PIB+ and PIB− patients as described above.

3.2. Relationship between K_1 and ePIB

Correlation analyses were performed across brain regions to evaluate the relationship between K_1 and ePIB. A significant positive correlation was found between K_1 and ePIB as shown in Fig. 1 ($r = 0.70$, $p<0.001$).

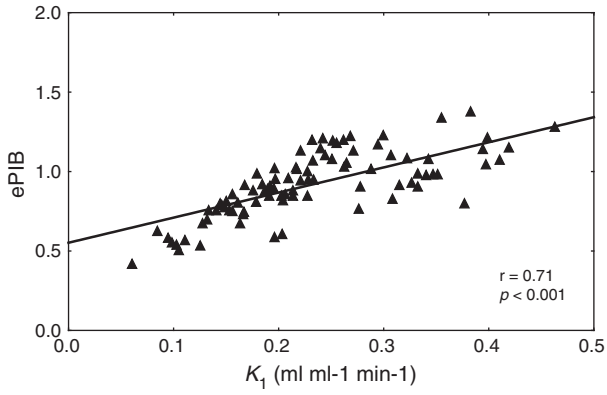

Fig. 1. Correlation across brain regions between the unidirectional influx K_1 and ePIB in 7 AD patients and 3 healthy controls. Included areas are frontal, parietal and temporal and primary visual cortices, putamen, thalamus, white matter and a ROI comprising the whole cortex at the level of thalamus.

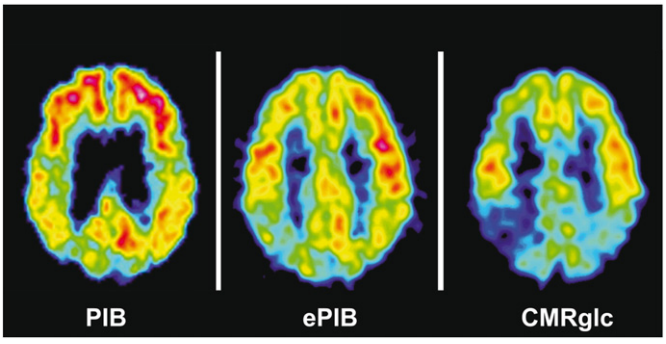

Fig. 2. Example of one AD patient showing high cortical PIB retention and clear parietal deficits in both relative cerebral metabolic rate of glucose (rCMRglc) measured by FDG-PET and ePIB (cerebral blood flow).

3.3. Group differences in PET parameters

The PIB+ group showed significantly higher PIB retention than the PIB− group dependent in all brain regions on the division of the material (Table 2). Significantly lower values of ePIB were solely observed in the PIB+ group compared to the PIB− group in the posterior cingulate cortex and parietal cortex (Table 2). The PIB+ group also showed significantly lower rCMRglc compared to PIB− group in all cortical brain regions as well as the striatum and thalamus but not in the white matter (Table 2).

3.4. Cerebral glucose metabolism (FDG) vs cerebral blood flow (ePIB)

The individual patients showed reduction in rCMRglc and ePIB uptake at visual inspection as exemplified in Fig. 2.

A positive correlation was found between rCMRglc and ePIB in all regions analysed (Table 3 and Fig. 3). The strongest correlations were found in the posterior cingulate cortex, parietal cortex, frontal cortex, primary visual cortex, and white matter respectively (Table 3 and Fig. 3).

3.5. Cerebral blood flow (ePIB) and cerebral glucose metabolism (FDG) compared with PIB retention

The cortical brain areas showed less correlation between ePIB and PIB retention compared to subcortical brain regions such as the striatum, and thalamus (Table 3).

Significant negative correlations between rCMRglc and PIB retention were observed in the posterior cingulate cortex, parietal and frontal cortices ($p<0.001$) (Table 3).

4. Discussion

Molecular imaging has advanced our knowledge of the time course of events leading to AD. Amyloid imaging has shown high accumulation of amyloid in very early state of disease and precedes functional changes measured as reduction in cerebral glucose metabolism and cognitive impairment [2]. Functional imaging using FDG-PET is clinically used to differentiate between different forms of dementia with specific decline in glucose metabolism in parietotemporal regions and posterior cingulate cortex [11,30] in AD patients. The same specific areas have shown decline in CBF [13]. It has also been indicated that there is a clear relationship between declines in glucose metabolism found with FDG-PET and decline in blood flow in AD patients [16]. The possibility to acquire functional and pathological information from a single dynamic PET scan might be valuable in the diagnosis of AD and in the evaluation of anti-amyloid treatment strategies.

In this study, we demonstrated that the unidirectional influx K_1 (reflecting the CBF) was significantly related to the ePIB ratio. This result supported our previous findings that K_1 is a good estimation of CBF [19], nevertheless ePIB should be appreciated as an estimation of CBF. These justified further exploration of the relationship between ePIB ratio, rCMRglc and CBF.

Pathological changes produced by amyloid depositions were measured with late PIB retention (PIB). Increased PIB retention was found in almost all AD patients, about half of the MCI patients and in one HC, which is supported by previous studies [1,3,4,31]. PIB+ MCI patients will most likely convert to AD in contrast to PIB− MCI patients [3]. In

Table 2
PIB retention, ePIB (early frames of PIB), and rCMRglc in patients with Alzheimer's disease (AD), mild cognitive impairment (MCI) and healthy controls (HC).

ROI	PIB			ePIB			rCMRglc		
	PIB−	PIB+	PIB− vs PIB+ *p*-level	PIB−	PIB+	PIB− vs PIB+ *p*-level	PIB−	PIB+	PIB− vs PIB+ *p*-level
Striatum	1.27 ± 0.12	2.16 ± 0.44	>0.001	1.09 ± 0.10	1.11 ± 0.10	0.490	2.00 ± 0.30	1.81 ± 0.26	0.012
Post cing	1.22 ± 0.16	2.33 ± 0.36	>0.001	1.03 ± 0.09	0.91 ± 0.12	>0.001	2.04 ± 0.44	1.40 ± 0.36	>0.001
WhM	1.70 ± 0.23	1.87 ± 0.24	0.009	0.54 ± 0.08	0.53 ± 0.08	0.598	0.88 ± 0.21	0.81 ± 0.16	0.187
Frontal ctx	1.17 ± 0.16	2.30 ± 0.41	>0.001	0.95 ± 0.07	0.93 ± 0.07	0.236	1.74 ± 0.31	1.48 ± 0.21	>0.001
Parietal ctx	1.30 ± 0.11	2.25 ± 0.35	>0.001	0.96 ± 0.07	0.87 ± 0.11	0.002	1.75 ± 0.29	1.25 ± 0.32	>0.001
Prim vis ctx	1.14 ± 0.10	1.84 ± 0.39	>0.001	1.07 ± 0.11	1.06 ± 0.11	0.556	1.84 ± 0.29	1.59 ± 0.27	0.002
Thalamus	1.36 ± 0.16	1.78 ± 0.31	>0.001	1.15 ± 0.10	1.15 ± 0.09	0.898	1.76 ± 0.21	1.59 ± 0.23	0.006
Temporal ctx	1.22 ± 0.10	1.77 ± 0.27	>0.001	0.78 ± 0.05	0.76 ± 0.06	0.234	1.29 ± 0.20	1.11 ± 0.15	>0.001

Post cing = posterior cingulate cortex, WhM = white matter, Prim vis = primary visual, ctx = cortex.

Table 3
Correlation between rCMRglc vs ePIB, ePIB vs PIB and rCMRglc vs PIB in patients with Alzheimer's disease (AD), mild cognitive impairment (MCI) and healthy controls (HC).

ROI	rCMRglc vs ePIB (n = 61)	ePIB vs PIB (n = 62)	rCMRglc vs PIB (n = 63)
Striatum	r = 0.27; $p = 0.035$	r = 0.33; $p = 0.008$	r = −0.18; $p = 0.152$
Posterior cingulate cortex	r = 0.74; $p < 0.001$	r = −0.26; $p = 0.045$	r = −0.53; $p < 0.001$
White matter	r = 0.63; $p < 0.001$	r = 0.20; $p = 0.127$	r = −0.20; $p = 0.124$
Frontal cortex	r = 0.42; $p = 0.001$	r = −0.02; $p = 0.879$	r = −0.41; $p = 0.001$
Parietal cortex	r = 0.74; $p < 0.001$	r = −0.27; $p = 0.032$	r = −0.51; $p < 0.001$
Primary visual cortex	r = 0.44; $p < 0.001$	r = 0.10; $p = 0.453$	r = −0.21; $p = 0.096$
Thalamus	r = 0.17; $p = 0.190$	r = 0.35; $p = 0.006$	r = −0.26; $p = 0.041$
Temporal cortex	r = 0.39; $p = 0.002$	r = 0.10; $p = 0.421$	r = −0.22; $p = 0.083$

the present study the MCI patients were slightly (but not significantly) younger that the AD patients. The PIB+ MCI patients may only underestimate their PIB retention at early stage of MCI when progression to late stages of MCI is expected [32]. Early frames of the same PIB-scan were compared with the glucose metabolism in AD patients, MCI patients and HC. Significant positive correlation between ePIB and the rCMRglc was demonstrated in all analysed areas, suggesting that early PIB frames might be used as a rough index of CBF. Due to the exploratory nature of the paper no corrections for multiple comparisons were performed and single correlations therefore need to be addressed with caution and rather the general patterns will be discussed. Nor did we study correlations in subgroups and further research needs to be done to address the relationship between these functional parameters.

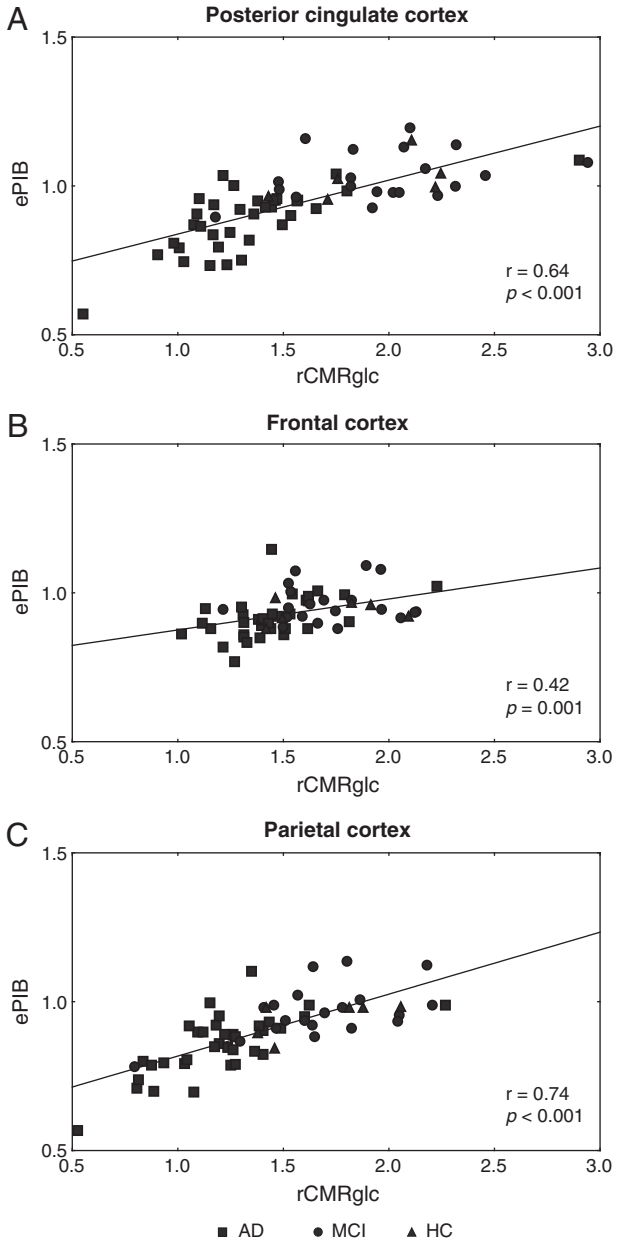

Fig. 3. Scatter plots of cerebral metabolic rate of glucose (rCMRglc) measured by FDG-PET and ePIB (cerebral blood flow). Correlation is found between rCMRglc and ePIB in all areas analysed and shown here is the posterior cingulate cortex (A), the frontal cortex (B) and the parietal cortex (C).

The rCMRglc however, seems to discriminate better than ePIB between PIB+ and PIB− patients. This could be explained by the fact that FDG-PET measures not only blood flow but neuronal and synaptic activity and a decrease indicates neuronal dysfunction [33], whilst decrease in CBF is a more indirect measurement of impairment caused by decreased demand of blood supply due to cerebral atrophy [34]. Evaluation of prognostic accuracy fell outside the scope of this paper and coming studies need to compare the prognostic accuracy of ePIB, CMRglc and CBF measured with conventional methods. However, the posterior cingulate cortex and the parietal cortex were areas that FDG-PET and ePIB-PET discriminated similarly between PIB+ and PIB− patients. A recent paper showed that the posterior cingulate cortex was the only hypometabolic area in all MCI subjects investigated in that study 35]. Hypometabolism or reduced CBF in parietotemporal regions and/or posterior cingulate cortex has been demonstrated to have predictor values in the conversion from MCI to AD [17,36,37]. It is valuable to combine these measurements with others, such as memory impairment 37,38] and structural imaging [39]. Multi-tracer PET studies can contribute to reveal the complex neuropathological processes of AD [2,40,41]. PIB retention seems to follow a different time course compared to that observed for cerebral glucose metabolism, cognition and brain atrophy [2,42]. Li et al. [43] suggested that the combination of data from PIB retention in the middle frontal gyrus with CMRglc in the hippocampus increases the correct classification of MCI patients vs HC from 75% and 85% respectively to 90% Lowe et al. [44] recently presented data indicating that PIB PET is better than FDG PET in discriminating between amnestic MCI and non-amnestic MCI [44]. The early and late frame ratios of PIB acquisitions provide complementary information that might improve the diagnostic power of PET. Early PIB uptake has been reported to positively correlate with MMSE score [45]. Furthermore Rostomian et al. [46] recently observed that early frames of PIB is slightly better than FDG in correctly classifying AD patients whilst both PET ligands are equally correct in classifying patients with frontotemporal lobe dementia [45].

In this study, we observed a significant correlation between rCMRglc and PIB retention in a data set from AD, MCI patients, and healthy controls This observations is in accordance with other studies suggesting some relation between pathological and functional parameters [1,47,48]. Only a few areas showed significant correlation between late PIB retention and ePIB and those included the thalamus and striatum. Nevertheless the r-values are really low witnessing of a big variance in the material and more research would be needed before drawing any further conclusions.

This study has the limitation of few subjects and further studies with larger number of patients are necessary to evaluate the diagnostic significance of blood flow measured with this method. This is a small explorative study suggesting the possibility to use cerebral blood flow estimated by early frame PIB data and their correlation to changes in rCMRglc. In order to test this hypothetical correlation we are utilising a data set with quite large variation in parameters in order to measure correlations. If the material had been divided into different individual groups we probably would have lost these correlations. In this study we do not draw any conclusions that ePIB can be used to show disease progression or to distinguish different patient groups. Although FDG-PET still is the method of choice to evaluate functional decline in brain the results in this study nevertheless it indicates that a single dynamic PIB PET may provide valuable information about pathological and physiological changes (amyloidosis and impaired blood flow) in AD. Such dual information could be used to better understand the pathology of dementia diseases hopefully contributing to improve future differential diagnosis also making it more cost effective with the need of only one PET scan. Clinical amyloid imaging will most probably be used as biomarkers when ^{18}F amyloid ligands will be clinically available. The new proposals of revised diagnostic criteria of AD from European efforts as well as the National Institute of Aging and Alzheimer's Association [49–53] suggest amyloid imaging as the early biomarker for prodromal AD. The use of these amyloid ligands as dual markers for both amyloid and functional (neuronal) changes will provide valuable clinical insight into the functional progression of the AD disease.

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