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Review

Pre-Clinical Detection of Alzheimer's Disease Using FDG-PET, with or without Amyloid Imaging

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Abstract. The development of prevention therapies for Alzheimer's disease (AD) would greatly benefit from biomarkers that are sensitive to subtle brain changes occurring in the preclinical stage of the disease. Early diagnostics is necessary to identify and treat at risk individuals before irreversible neuronal loss occurs. *In vivo* imaging has long been used to evaluate brain structural and functional abnormalities as predictors of future AD in non-demented persons. Prior to development of amyloid-β (Aβ) tracers for positron emission tomography (PET), the most widely utilized PET tracer in AD was 2-[18F]fluoro-2-Deoxy-D-glucose (FDG) PET. For over 20 years, FDG-PET has been used to measure cerebral metabolic rates of glucose (CMRglc), a proxy for neuronal activity, in AD. Many studies have shown that CMRglc reductions occur early in AD, correlate with disease progression, and predict histopathological diagnosis. This paper reviews reports of clinical and preclinical CMRglc reductions observed in association with genetic and non-genetic risk factors for AD. We then briefly review brain Aβ PET imaging studies in AD and discuss the potential of combining symptoms-sensitive FDG-PET measures with pathology-specific Aβ-PET to improve the early detection of AD.

Keywords: Amyloid-β, cerebral metabolic rate of glucose (CMRglc), normal aging, positron emission tomography, preclinical detection

INTRODUCTION

Alzheimer's disease (AD) is becoming an increasingly important reason for concern for healthcare and society. AD is the most common form of dementia, affecting approximately 10% of individuals 65 years of age, with the prevalence doubling every 5 years up to age 80, above which the prevalence exceeds 40% [1]. In 2007, there were more than 26.6 million people affected by AD in the world [2]. The prevalence of AD is estimated to be further increasing in the next few years, as the baby-boomers generation ages [3]. The main reason for increasing prevalence in AD is the lack of disease-modifying treatments. Once disease-modifying drugs become available, they will likely be most effective if administered early in the course of disease, before irreversible brain damage has occurred. Therefore, another major problem in AD is the lack of diagnostic markers, especially for the early stages of disease when clinical symptoms are not clearly ex-

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pressed. Detection of preclinical pathological modifications in the brain is likely the key to identify individuals bound to develop AD.

Brain imaging, among other techniques, is a promising tool for the early detection of AD. Changes in brain histopathology, and consequently in its structure and function, are known to precede the clinical manifestations of disease by many years. These modifications can be visualized *in vivo* using brain imaging modalities. In chronological order, computerized tomography (CT) came first, followed by magnetic resonance (MR), and positron emission tomography (PET) with functional tracers such as 2-[^{18}F]fluoro-2-Deoxy-D-glucose (FDG), and to a lesser extent with receptor ligands. Not yet 10 years ago, PET tracers for fibrillar amyloid-β (Aβ), the principal constituent of AD senile plaques, have been developed, which made detection of AD pathology *in vivo* a reality. Presently, many AD clinical and research centers perform Aβ PET imaging, and an effort has been made in the United States to receive FDA approval for amyloid PET ligands in the diagnosis of AD and other dementias. However, the petition was rejected considering that detection of Aβ would not be specific for an AD diagnosis, based on the observation that many elderly with Aβ plaques never develop dementia and that other dementias share similar pathological substrates [4]. Much remains to be learned about fibrillar Aβ as a biomarker for AD, especially at the early stages of disease. Prior to development of Aβ PET tracers, FDG-PET was the most widely used PET technique in AD. For over 20 years, FDG-PET has been used to measure cerebral metabolic rates of glucose (CMRglc), a proxy for neuronal activity, in clinical AD patients and in at risk individuals. The present paper reviews FDG-PET findings in the early detection of AD, and discusses the value of performing FDG-PET with or without amyloid imaging.

WHY WE NEED BRAIN IMAGING FOR THE EARLY DETECTION OF AD

AD is a neurodegenerative disorder with insidious onset and progressive declines in memory, attention, and language [5]. Currently, the provisional diagnosis of AD remains based on clinical history, neurological examination, cognitive testing, and structural neuroimaging, while the definitive diagnosis of AD is based on the postmortem detection of specific pathological lesions: Aβ plaques in the extracellular space and blood vessels, intracellular neurofibrillary tangles (NFT), and neuronal and synaptic loss in specific brain regions [6]. There are no tests for the definitive diagnosis of AD *in vivo*. Ironically, we ultimately define the disease with pathological criteria, but we have hardly any information in this regard during life. As a result, patients may be misdiagnosed with AD when in fact they have another dementia or may be left undiagnosed [7]. The lack of standardized diagnostic tests for AD greatly limits the potential for an accurate diagnosis, and even more so, for early detection.

The problem is not what to measure, but how to measure it. Once the 'how' is resolved, the next question is when – how early in life can we detect clear-cut signs of an ongoing neurodegenerative process distinct from normal aging. Neurodegeneration in AD is estimated to begin 20–30 years before the clinical manifestations of disease become evident [8–11]. According to a popular theoretical model in AD, the "amyloid cascade hypothesis" [12], during this preclinical phase, Aβ plaques and NFT load increase, causing synapse loss and neuronal death. In light of recent findings that Aβ fibrils do not appear to be the main promoter of neuronal degeneration [12], the amyloid hypothesis was reformulated by stating that Aβ oligomers confer neurotoxicity to neurons by disrupting nerve signaling pathways in AD [13,14].

While the causes of AD are being investigated, consensus exists as to where neurodegeneration strikes first in AD. The medial temporal lobes (MTL, i.e., hippocampus, transentorhinal/entorhinal cortex, and subiculum), which are critically involved in the neural control of memory functions, are most vulnerable to AD pathology [9,11,15–17]. The posterior cingulate, parieto-temporal, and frontal cortices become affected later in the course of disease, in keeping with progression of clinical symptoms [9,11,15–17]. The local and distant effects of AD pathology on tissue physiology impair neuronal function in these vulnerable regions [18], causing cognitive impairment and dementia [19]. While postmortem staging is based on cross-sectional detection of different patterns of anatomical involvement across subjects with different levels of dementia severity, longitudinal imaging studies enabled us to characterize the temporal progression of these regional brain deficits in the same individual, as discussed below.

WHY WE HAVE BEEN USING FDG-PET IMAGING

The early appearance of pathological lesions and the progressive nature of cognitive deterioration in AD in-

dicate a great need for developing biological markers of disease, sensitive to early, longitudinal changes. Until 10 years ago, when Aβ PET imaging was developed, other technologies had to be used to measure surrogate markers of AD pathology. The most readily available techniques were magnetic resonance imaging (MRI), which is used to measure structural tissue loss (i.e., atrophy), and FDG-PET to measure the functional effects of neuronal activity at the tissue level.

A growing list of observations has highlighted the importance of FDG-PET as a tool to distinguish AD from other dementias, predict and track decline from normal cognition to AD, and to identify individuals at risk for AD prior to the onset of cognitive symptoms. What we have learned from over 30 years of FDG-PET research in AD is that, first of all, AD is characterized by a specific regional pattern of CMRglc reductions. AD patients show consistent CMRglc deficits in the parieto-temporal areas [20,21], posterior cingulate cortex (PCC) [22], and MTL [23]. As the disease progresses, frontal association cortices become involved, while cerebellum, striatum, basal ganglia, primary visual, and sensorimotor cortices remain preserved [21,23]. The extent and regional distribution of hypometabolism may vary across subjects, and hemispherical asymmetries are often noted [23,24], especially at the early stages of AD. Asymmetries are often detected in clinical practice and may be attributed to co-morbidity factors (e.g., vascular brain disease) or compensatory mechanisms (e.g., neuroplasticity), which would not be easily revealed by AD pathology imaging. This *in vivo* pattern of hypometabolism is found in the vast majority of clinically diagnosed AD patients and in over 85% pathologically confirmed AD cases [21].

CMRglc is highly correlated with clinical disabilities in dementia [25]. Clinical AD symptoms essentially never occur without CMRglc decreases, the extent of which is related to the severity of cognitive impairment [26–29]. Moreover, despite some overlap, the characteristic AD-pattern of CMRglc reductions yields high sensitivity in distinguishing AD from controls [30,31], from other neurodegenerative dementias, such as frontotemporal (FTD) and Lewy body dementia (DLB) [21,31], and from cerebrovascular disease [32]. In a large multi-center study of normal (NL), AD, FTD, and DLB subjects, individual FDG-PET scans were processed using automated voxel-based methods to generate disease-specific patterns of regional FDG uptake [31]. These standardized disease-specific PET patterns correctly classified 95% AD, 92% DLB, 94% FTD, and 94% NL [31]. The method yielded high discrimination accuracy in patients with mild dementia as well as moderate-to-severe dementia [31]. Altogether, these findings support the use of FDG-PET in the differential diagnosis of the major neurodegenerative dementing disorders.

Second, CMRglc reductions on FDG-PET precede the onset of AD symptoms in predisposed individuals, in both genetic early-onset and late-onset AD forms. FDG-PET findings in preclinical AD are summarized in Table 1. Presymptomatic persons carrying autosomal dominant genetic mutations associated with early onset familial AD (EOFAD, onset age $<$ 65 yrs) show the typical AD pattern of hypometabolism compared to age-matched mutation non-carriers [33–35]. FDG-PET abnormalities were observed up to 13 years prior to the onset of symptoms in EOFAD subjects [35]. While findings in EOFAD may not apply to the more common forms of late-onset AD, studies of patients with mild cognitive impairment (MCI) have reported similar evidence for presymptomatic CMRglc reductions. Among MCI patients, those presenting with more pronounced, or more AD-like, CMRglc reductions decline to AD at higher rates than those who do not show hypometabolism [22,36–38]. CMRglc reductions in MCI predict future AD with 75%–100% accuracy [22,36–41]. While early and late onset AD may or may not share a common pathology [12], FDG-PET studies have identified a similar outcome pattern of hypometabolism that appears to be a prodromal "metabolic signature" of AD independent of the age at onset of disease. More studies are needed to examine and compare the mechanisms underlying CMRglc reductions in the early and late onset AD.

A few FDG-PET showed an even earlier prediction capacity at the normal stages of cognition. By monitoring progression to MCI and AD among cognitively normal (NL) elderly, these studies showed that CMRglc reductions precede the onset of dementia by many years [42–45], and predict cognitive decline from NL cognition to MCI/AD with over 80% accuracy [42, 43]. The decliners to MCI and AD showed greater rates of CMRglc reductions as compared to the non-decliners [38,42–45]. Progressive CMRglc reductions were observed years in advance of clinical symptoms in a clinico-pathological series of subjects followed with longitudinal *in vivo* FDG-PET scans from normal cognition to the clinical diagnosis and to post-mortem confirmation of AD [45].

More work is needed to establish how early FDG-PET deficits become detectable in the course of dis-

Table 1

FDG- and PIB-PET findings in preclinical AD

At-risk group	Control group		FDG-PET findings vs. controls	References	PIB-PET findings vs. controls	References
Presymptomatic Early-onset Familial AD	Mutation Non-carriers	Cross-sectional	– Whole brain hypometabolism – Parieto-temporal, PCC, frontal cortex, and MTL hypometabolism	33	– Higher PIB retention in striatum	71, P 105 106
		Longitudinal	– Greater CMRglc declines over time	33	N.A.	
NL decliners to MCI and to AD	Stable NL	Cross-sectional (baseline data predicts clinical change)	– MTL hypometabolism when NL – Parieto-temporal and PCC hypometabolism at time of decline to MCI/AD	42	N.A.	
		Longitudinal	– Greater CMRglc declines over time	43	N.A.	
MCI decliners to AD	Stable MCI	Cross-sectional (baseline data predicts clinical change)	– Parieto-temporal, PCC and frontal cortex hypometabolism	22	– Higher PIB retention in PCC and frontal cortex – Higher cortical FDDNP binding	80 89
		Longitudinal	– Greater CMRglc declines over time	38	– Increases in cortical FDDNP binding	89
NL with Subjective Memory Complaints	NL without Subjective Memory Complaints	Cross-sectional	– Parieto-temporal and MTL hypometabolism	48	N.A.	
		Longitudinal	N.A.		N.A.	
NL ApoE-4 Carriers	NL ApoE-4 Non-carriers	Cross-sectional	– Parieto-temporal, PCC, thalamus, and frontal cortex hypometabolism – Greater CMRglc declines over time	49	– Higher PIB retention in frontal, temporal, PCC/precuneus, parietal cortex and basal ganglia	83
		Longitudinal		51,52	N.A.	
NL Kibra CC carriers	NL Kibra CT and TT carriers	Cross-sectional	– PCC/Precuneus hypometabolism	55	N.A.	
		Longitudinal	N.A.	N.A.	N.A.	
NL with a 1^{st} degree family history of late onset AD	NL with negative family history of AD	Cross-sectional	– Parieto-temporal, PCC, frontal cortex, and MTL hypometabolism in NL with AD mothers as compared to those with AD fathers and to those with no parents with AD	56	N.A.	
		Longitudinal	– Greater CMRglc declines over time in NL with AD mothers as compared to those with AD fathers and to those with no parents with AD	57	N.A.	

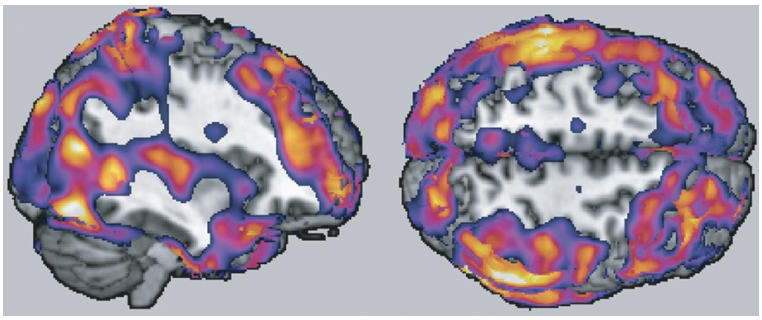

Fig. 1. Brain regions showing reduced CMRglc on FDG-PET in cognitively normal individuals with a maternal family history of AD as compared to demographically matched subjects with a paternal family history and with a negative family history of AD [57]. Statistical parametric maps showing regions of hypometabolism in NL individuals with a maternal history of AD are displayed on a purple-to-yellow color coded scale at $P < 0.001$. Figure shows the left lateral and superior views of a 3D volume-rendered MRI.

ease. Nonetheless, published studies show that non-demented individuals with reduced CMRglc are at increased risk for developing AD, which supports the use of FDG-PET in the early detection of AD.

CMRglc deficits resembling those in clinical AD patients have been observed in NL individuals at clinical or genetic risk for AD. With respect to AD risk established on clinical grounds, cognitively normal individuals with subjective memory complaints are regarded as a group at increased risk for dementia [46, 47]. On FDG-PET, middle-age to old normal individuals with subjective memory complaints showed CMRglc reductions in AD-vulnerable brain regions as compared to demographically matched individuals with no such complaints [48]. With respect to genetic risk factors for late-onset AD, many studies have shown that non-demented individuals carrying an apolipoprotein E (ApoE) ε4 allele have CMRglc reductions as compared to ApoE ε4 non-carriers [49–53]. CMRglc deficits in NL ApoE ε4 carriers are progressive, correlate with reductions in cognitive performance [49,52], and occur in young adulthood [53]. Likewise, NL carriers of the KIBRA CC haplotype, a risk factor for memory impairment in late life [54], showed CMRglc reductions as compared to low-risk KIBRA TT and CT carriers [55].

First degree relatives of AD patients also appear to be at high risk for late onset AD. In particular, a maternal history of AD was shown to affect brain metabolism in NL individuals [56,57]. CMRglc deficits in AD-vulnerable regions were observed in NL with a maternal family history of AD as compared to those with a paternal history and those with no family history of AD (Fig. 1) [56]. Interestingly, NL with AD fathers did not show CMRglc abnormalities [56]. Over a 2-year period, NL individuals with an AD mother showed progressive declines in regional CMRglc compared to those with no parents with AD as well as to those with an AD father [57]. The genetic mechanisms that underlie maternally inherited CMRglc reductions are under investigation [58]. More studies are needed to replicate these first reports and to identify the genetic factors involved in hypometabolism in preclinical AD.

Overall, the major strengths of FDG-PET in AD can be summarized as: high sensitivity to distinguish AD from controls and from other neurodegenerative diseases, and individuals at higher versus lower AD risk, and good quantitative and topographical correlation with clinical progression. However, a major limitation to most of the above FDG-PET studies is the absence of postmortem data. Doubt remains as to whether clinical symptoms and CMRglc reductions are due to AD pathology or to other causes. Using clinical diagnosis as the gold-standard may lead to erroneously include patients with a dementia other than AD in the AD group, and vice versa. In asymptomatic subjects showing hypometabolism, CMRglc deficits may develop for reasons other than AD, and not all subjects showing hypometabolism will necessarily decline to AD. Here is where, in our opinion, imaging of AD pathology plays an essential role.

WHEN FDG-PET ALONE IS NOT ENOUGH, AND THE ADVENT OF AMYLOID PET TRACERS

Several PET tracers for Aβ plaques have been developed in the last few years. The best known tracers are N-methyl-[^{11}C]2-(4'-methylaminophenyl)-6-hydroxybenzothiazole, aka Pittsburgh Compound-B (PIB) [59], 4-N-[^{11}C-methyl]amino-4'-hydroxystilbene (SB13) [60], 2-(1-96-(2-^{18}F-fluoroethyl)(methyl)

amino)-2-naphthyl)ethyldene)malono nitrile (FDDNP) [61], and more recently the *trans*-4-(N-methyl-amino)-4'-{2-[2-(2-[18F]fluoro-ethoxy)-ethoxy]-ethoxy}- stilbene (BAY94-9172) [62]. Among these tracers, PIB is the most widely utilized and best characterized in terms of tracer kinetics, modeling, and analytic methods. PIB binds to fibrillar Aβ plaques with high affinity [63]. Several PIB-PET studies demonstrated significant PIB retention in AD patients as compared to controls, mostly in the frontal cortex, parieto-temporal, PCC/precuneus, occipital lobes, thalamus, and striatum [63–67], consistent with the known pattern of Aβ plaques deposition observed at postmortem. Significant PIB retention is found in over 90% clinically diagnosed AD patients, in as many as 60% of MCI [65,64, 66–70], and 30% of NL elderly [67]. PIB-PET showed higher Aβ load in asymptomatic and symptomatic individuals carrying presenilin-1 (PSEN1) and AβPP mutations as compared to controls [71]. PIB retention was especially high in the striatum of mutation carriers as compared to controls and to sporadic AD patients [71]. These findings suggest that the striatum may be more affected in early onset AD and the neocortex in the late onset AD forms.

Interestingly, patients can be easily dichotomized as showing either significant (PIB+) or absent PIB retention (PIB-), but hardly show intermediate levels [65,64, 66–70]. This could facilitate interpretation of PIB-PET scans for clinical use. The presence of a PIB+ pattern has been shown to improve the differential diagnosis of AD from FTD and from Parkinson's disease [67, 72]. However, significant PIB retention is observed in DLB [64], and in patients with cerebral amyloid angiopathy (CAA) [73]. The impact of vascular amyloid on PIB signal is particularly relevant in view of using PIB, or other Aβ tracers, in the early detection of AD. A study showed that PIB is not specific for dense, classical plaques [74], but rather binds to a family of amyloid substrates ranging from diffuse plaques to plaques in the vascular system (i.e., CAA) [75].

Vascular pathology is common in the elderly, and it is not known how much of the PIB retention observed in NL elderly is due to vascular Aβ deposits. Moreover, it is known from postmortem studies that typical amyloid and NFT lesions are found in both demented and non-demented individuals [10,11,76–78]. Non-demented cases with substantial AD pathology are often described as a 'preclinical' AD group given the absence of cognitive abnormalities [10,78]. This observation brings up the important, and often overlooked, discrepancy between AD-pathology and AD-dementia [79]. Those NL and MCI showing an AD-like PIB pattern (and therefore Aβ pathology) are conceivably at higher risk for developing AD-dementia as compared to individuals without brain Aβ pathology. However, having Aβ plaques does not equal to being at a 'pre-dementia stage', and the prognostic value of increased Aβ load on PET has to be established. Since Aβ imaging is a relatively new technique, there are not enough published longitudinal PIB-PET studies to draw conclusions on its preclinical value in AD (Table 1). A few studies in MCI have shown that, at baseline, those MCI who later declined to AD showed higher PIB retention as compared to the non-decliners [80–82]. There are no published PIB-PET reports in NL individuals declining to AD. A recent PIB-PET study in middle aged to old NL individuals showed significantly higher PIB retention in NL ApoE ε4 carriers compared to non-carriers [83]. Although the predictive value of PIB abnormalities in the asymptomatic ApoE ε4 carriers is not known, PIB measures may be useful to discriminate NL individuals at higher versus lower risk for AD [83].

However, the correlation between PIB retention and cognition is generally fairly weak [84], consistent with the notion that Aβ plaques distribution does not correlate with clinical symptoms in AD [85]. Additionally, the few published longitudinal PIB-PET papers indicate a lack of progression of PIB uptake in NL, MCI, and AD [86–88]. AD patients apparently reach a plateau in PIB retention, despite progression of their clinical symptoms and worsening of hypometabolism on FDG-PET [86]. Jack and colleagues [87] examined longitudinal PIB-PET in NL, MCI, and AD and showed that the rate of PIB change did not differ by clinical group. The lack of longitudinal progression suggests that PIB deposition could be an early event during aging and disease. Otherwise, lack of change suggests that PIB and similar tracers may not be the best option for longitudinal studies (discussed below). In this respect, FDDNP appears to have an advantage over PIB, since FDDNP studies showed some longitudinal effects [61]. FDDNP binds both Aβ fibrils and NFT, and shows a cortical binding pattern similar to PIB, and additionally binds to the MTL [61,89]. Moreover, MCI patients showed intermediate FDDNP levels between NL and AD, demonstrating finer grading than PIB measures [89]. FDDNP uptake was highly correlated with scores on memory and global cognition [89]. Although limited by the small sample, longitudinal progression effects were reported for 3 non-demented subjects that deteriorated over 2 years, including one subject that

declined from NL to MCI, and 2 MCI that converted to AD [89]. The major limitation to using FDDNP is the low specific to non-specific binding ratio of the tracer [61,89] which makes these scans difficult to interpret for clinical use.

USING FDG-PET WITH OR WITHOUT AMYLOID IMAGING FOR THE EARLY DETECTION OF AD

Given the low specificity of FDG-PET for AD pathology, the addition of amyloid PET tracers may be useful in the early detection of AD. An effective strategy to increase the preclinical diagnostic accuracy would be to combine the sensitivity of FDG-PET with pathology-specific Aβ measures.

For clinical purposes, amyloid-PET appears to be most useful to distinguish AD from non-amyloid dementias, such as FTD. Such capacity may prove particularly useful at the mild stages of dementia, when symptoms are not fully expressed, and FDG-PET scans may not show clear-cut regional metabolic abnormalities. Amyloid imaging would be suitable to rule out AD in the presence of a PIB- scan, since a demented patient without brain Aβ cannot have AD-dementia by definition. However, amyloid imaging may not be sufficient to rule in AD. If a patient with uncertain diagnosis is PIB+, it would not possible to distinguish between AD, DLB, and CAA based on PIB alone.

Diagnosis of AD at early stages of dementia would be more problematic because many NL elderly with brain Aβ deposits never develop dementia in life [90]. Amyloid imaging is necessary for the early detection of Aβ pathology, but may not be sufficient to make an early diagnosis of AD-dementia. Histology studies have shown that, among individuals with AD pathology, what differentiates demented from non-demented subjects is the presence of neuronal loss. In general, non-demented subjects with AD pathology do not show neuronal loss at postmortem, while demented subjects with AD pathology show decreases in neuronal number and volume [90]. These findings indicate that neuronal degeneration is a stronger predictor of dementia than AD pathology [90]. Therefore, functional tracers like FDG-PET, whose signal correlates well with cognitive impairment, may be needed to appreciate the extent to which Aβ is affecting brain function. Non-demented individuals showing increased Aβ load and reduced CMRglc would be the ideal target population for prevention studies in AD (Fig. 2).

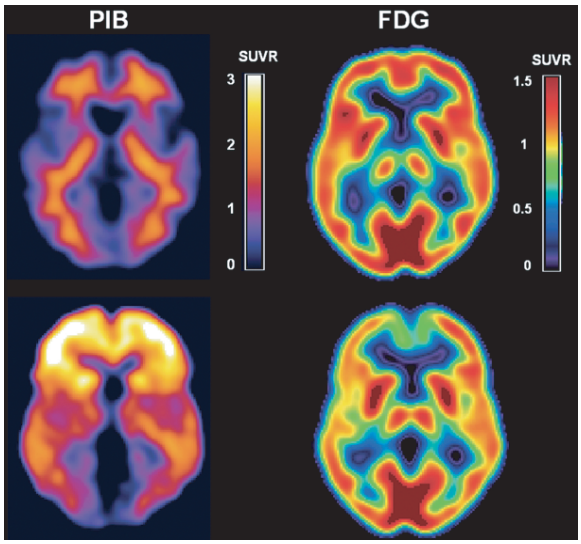

Fig. 2. Coregistered PIB and FDG-PET scans in 2 representative cognitively normal individuals at conceivably low risk for AD (top row: negative PIB and normal FDG uptake), and at high risk for AD (bottom row: positive PIB and reduced FDG uptake) based on PET imaging findings. Cerebral-to-cerebellar PIB Standardized Uptake Value ratios (SUVR) are displayed for each modality using a color coded scale.

FDG-PET studies have shown preclinical CMRglc abnormalities in individuals in their 40's [53]. It is not known how early in the course of disease Aβ depositions can be detected. Except for the known presence of amyloid deposits in young individuals with Down's syndrome [91,92], Aβ plaques are more prevalent in brains of individuals older than age 50 years [93,94]. It was hoped that Aβ imaging would facilitate the study of the time course of amyloid deposition in brain. However, people appear to either have substantial brain Aβ or not and remain relatively unchanged over time. This could be due to the fact that Aβ deposition is a very early event in AD. Should this be the case, then amyloid tracers may be more useful for longitudinal examination of younger individuals with minimal tracer uptake, who may still show progression effects. Otherwise, lack of effects could be due to technical issues, such as the intrinsically low spatial resolution of PET scanners, or to the fact that PIB uptake reflects the presence of Aβ fibrils, but not fibrils' dimension or growth [95,98]. Ever since the first validation studies [96,97], PIB analysis has been based on simplified reference tissue models from receptor studies, which treat Aβ, a polymer, as if it were a receptor [98]. There is a conceptual difference between imaging the density of Aβ fibril polymers and neuronal receptors. Based on this observation, the concept of Aβ molecular imaging probes was introduced

as a new paradigm that goes beyond classic binding potential parameters to include binding characteristics to polymeric peptide aggregates [95,99]. This would ideally increase resolving power in characterizing the progression of Aβ, especially for subjects presenting with substantial uptake at the first examination.

The exact role played by Aβ plaques in AD is not clear. Recent studies have shown that Aβ dimers and oligomers, not plaques, promote neuronal degeneration [12,13,100,101]. Aβ plaques represent a fraction of total Aβ in the brain that has been condensed and neutralized, and no longer contributes to neurotoxicity [101]. Measurement of soluble Aβ is needed to correctly estimate risk for developing AD, but tracers for soluble Aβ are not available. Measurement of fibrillar Aβ, as achieved with PET, could be seen in two opposing ways: either as an index of how much soluble Aβ the brain has been dealing with, and therefore as a sign of increased risk, or as an index of how well the brain has been getting rid of toxic Aβ, and therefore as a sign that the brain is strong enough to cope with the bad Aβ. There is evidence that highly educated AD patients show increased PIB uptake and lower CMRglc as compared to patients with low education, but with a similar degree of cognitive impairment [102, 103]. The results support the hypothesis that 'cognitive reserve' influences the association between Aβ pathology and cognition [102,103]. The question of whether Aβ predisposes to AD-dementia will be answered once treatment against fibrillar Aβ becomes available.

Finally, in the enthusiasm of being able to image Aβ *in vivo*, NFT have been somewhat neglected. While the relationship between these two abnormal proteins in AD is still under investigation [85,100], the diagnosis of AD remains based on the presence of both plaques, NFT, and neuronal loss with a specific neuroanatomy. Imaging NFT is particularly important as NFT progression follows the expected pattern of regional involvement based on clinical symptoms [11], and unlike Aβ plaques, NFT load correlates with cognitive impairment in AD [104]. *In vivo* imaging of NFT is still under development.

In conclusion, much research has been done with FDG-PET in AD since the first studies in the 1980s. Thanks to the technique's sensitivity to progression effects, FDG-PET is a candidate modality for detecting functional brain changes in early AD. Technical improvements, particularly the enhanced resolution of modern PET-CT and HRRT scanners, have led to increased anatomical accuracy, providing the possibility to detect energetic changes within the neuro-vascular unit, as well as to identify "specific" patterns of cortical and subcortical hypometabolism to distinguish AD from other dementias at an early stage [107]. Nonetheless, there remains a great need to increase preclinical diagnostic specificity.

It is possible that the combination of dementia-sensitive CMRglc with pathology-specific Aβ and NFT imaging would improve the early, differential diagnosis of AD. Additional validation studies are needed before Aβ PET imaging can enter into clinical practice, and more longitudinal studies are necessary to establish the limits and strengths PET for early diagnosis of AD. Accurate characterization of the extent and nature of brain damage in individual patients, based on converging evidence from different biomarkers, will likely play an important role in the prediction of subjects' clinical course. Other potential benefits include the selection of individualized treatment plans and screening of patients with more uniform underlying pathology for targeted research and drug trials. Hopefully, continued technological progress will one day allow us to image all aspects of AD pathology *in vivo*, at proper microscopic resolution, without the need for invasive procedures.

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