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PET Amyloid-Beta Imaging in Preclinical Alzheimer's Disease

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Alzheimer's disease (AD) is the leading cause of dementia, accounting for 60–70% of all cases [1]. The need for effective therapies for AD is great. Current approaches, including cholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists, are symptomatic treatments for AD but do not prevent disease progression. Many diagnostic and therapeutic approaches to AD are currently changing due to the knowledge that underlying pathology starts 10 to 20 years before clinical signs of dementia appear [2]. New therapies which focus on prevention or delay of the onset or cognitive symptoms are needed. Recent advances in the identification of AD biomarkers now make it possible to detect AD pathology in the preclinical stage of the disease, in cognitively normal (CN) individuals; this biomarker data should be used in the selection of high-risk populations for clinical trials. *In vivo* visualization of AD neuropathology and biological, biochemical or physiological confirmation of the effects of treatment likely will substantially improve development of novel pharmaceuticals. Positron emission tomography (PET) is the leading neuroimaging tool to detect and provide quantitative measures of AD amyloid pathology *in vivo* at the early stages and follow its course longitudinally.

Aβ metabolism

Although the exact cause-and-effect relations in AD are not well understood, several potential underlying abnormalities have been suggested including increased production, misfolding and deposition of proteins; disruption of receptor and neurotransmitter state; changes in synaptic density and functioning; and eventually degeneration and death of neurons with resultant brain atrophy [3–6].

Pathologically, AD primarily is characterized by the presence of two abnormal proteins in the aggregated state: extracellular plaques composed of beta-amyloid (Aβ) and intraneuronal neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau [7]. The Aβ peptide is cleaved by different secretases from the transmembrane protein amyloid precursor protein (APP). When normally soluble Aβ proteins reach a critical concentration, they become insoluble, misfold, and aggregate in the form of Aβ plaques. Distinct plaque subtypes have been identified: those with low (diffuse plaques) and high (cored or neuritic plaques)

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proportion of fibrillar components [8]. Insoluble Aβ exceeds soluble forms of Aβ by a factor of about 100-fold in AD brain [9]. Studies of immunotherapies in transgenic mice [10, 11] and autopsy studies of humans treated with active immunization in the AN-1792 trial [12–14] indicate that Aβ in fibrillar plaques can be mobilized and cleared.

Plaques are composed of insoluble Aβ peptides, mostly 42 amino acids in length (Aβ-42) [15]. It is possible that the small aggregated oligomeric forms of Aβ-42, rather than fibrils or plaques, are the key pathological substrates [16].

It should be noted that in rare cases of AD, genetic alterations increase the production of Aβ [17]. However, impaired clearance of Aβ may cause late-onset AD through interactions with apolipoprotein E (APOE) ε4, decreased catabolism of Aβ through reduced proteolysis, impaired transport across the blood-brain barrier, or impaired CSF transport [18].

Aβ cascade hypothesis

Characterization of the initial deposition of Aβ plaques is important to improve our understanding of the pathology of early AD. The amyloid-cascade hypothesis suggests that APP mismetabolism and subsequent Aβ aggregation are the primary events driving AD pathogenesis [19–21]. High levels of Aβ subsequently lead to a series of downstream pathological events, including the production of extensive intracellular NFT deposits, inflammation, oxidative stress, excitotoxicity, loss of synaptic connections, and cell death, which cause the clinical manifestations of AD. Multiple causative factors may be involved [2, 22–24]. Mutations in the Aβ precursor protein gene on chromosome 21, all lying in or near the Aβ peptide region, cause early-onset, autosomal dominant familial forms of AD [25–27]. Presenilin-1 [28] and presenilin-2 [29] are other two genes that encode highly homologous transmembrane proteins, in which multiple mutations have been identified in familial early-onset and late-onset AD [30]. In addition to potentially harmful effects of Aβ for brain cells [31], increased synaptic activity can elevate soluble Aβ levels [32] and neural activity can change levels of APP [33], which suggests that Aβ production and soluble levels may be in a dynamic equilibrium state.

A close relationship between synaptic activity, brain metabolism and Aβ deposition has been recently advocated by the results of a study which observed a high spatial correlation between the pattern of Aβ deposition in patients with dementia of Alzheimer type (DAT) patients and the pattern of aerobic glycolysis measured using combined glucose and oxygen metabolism PET studies in healthy young adults [34]. These data indicate that when Aβ accumulates in the human brain in AD, it does so in a distribution that closely mirrors that of elevated aerobic glycolysis in the resting state of healthy young adults [34, 35]. Strong correlation between aerobic glycolysis and Aβ deposition was demonstrated not only in DAT patients but also in CN individuals with abnormally elevated levels of Aβ, which indicate that these CN individuals may be at the earlier stage of pathological processes seen in the DAT group [34], the stage which is considered to represent preclinical AD [36].

Even if Aβ is not the only or even the main causal event in AD pathology, the deposition of Aβ is likely important for signifying the beginning of the pathological cascade. Since all young healthy persons and many CN older individuals have no evidence of Aβ deposition, the conversion of a non-demented person from no evidence of Aβ plaques to Aβ deposits in a cerebral distribution corresponding to that seen in advanced DAT suggests a pathological event. We believe that the pathological cascade may eventually become irreversible and independent of the availability and level of Aβ, however we do not know at what stage of AD this irreversibility may be achieved. Thus, it is critical to find better tools for determination of optimal timing for interventions aimed on decreasing Aβ level and

especially those which may prevent irreversibility and further progression of pathological cascade.

Biomarkers of AD

Biomarkers provide unique, biological measure of the underlying pathology independent of clinical signs and neuropsychological characteristics of AD, and identification of reliable biomarkers is critical for evaluation of the preclinical/asymptomatic state of the AD. To date, the most widely studied and best validated biomarkers include cerebrospinal fluid (CSF) assays of Aβ and tau, and amyloid imaging with N-methyl-[^{11}C]2-(4=-methylaminophenyl)-6-hydroxybenzothiazole (Pittsburgh Compound B, or [^{11}C]PIB) [2, 37–39]. In addition, decreased glucose metabolism in temporal and parietal cortex is considered as a biomarker of synaptic dysfunction (commonly seen in the symptomatic phase of AD). Similarly, brain atrophy in the medial temporal lobes, paralimbic, temporal and parietal cortex on structural MRI is a biomarker of AD-related neurodegeneration, also commonly seen during the symptomatic phase of AD. Recently a biomarker model has been recently proposed which suggests an ordered manner of abnormalities of these biomarkers which parallels the hypothetical pathophysiological sequence of AD and is particularly relevant to tracking the preclinical stages of AD [39, 40].

Levels of CSF Aβ42 are commonly decreased in patients with AD [41]. In a study comparing fluid and imaging measures of potential preclinical biomarkers of AD pathology, a robust relationship was observed between cortical [^{11}C]PIB binding and levels of CSF Aβ42 in CN individuals [42, 43]. Individuals with high cortical Aβ as detected by [^{11}C] PIB PET had low CSF Aβ42 whereas those without cortical Aβ had high Aβ42. These findings suggest that a low CSF Aβ42 level is a sensitive marker of Aβ deposition in the brain regardless of the state of AD.

It should be noted that decreased CSF Aβ42 levels have also been reported in frontotemporal dementia, vascular dementia, Creutzfeldt-Jacob disease and dementia with Lewy bodies [44–46]. Potential limitation of AD studies that have used CSF Aβ42 is the lack of standardization for Aβ quantification. Little is known about the CSF Aβ42 turnover and clearance in normal aging, and known circadian fluctuations of CSF Aβ42 levels [47] may possibly contribute to the variability of results. Levels of CSF Aβ42 do not correlate well with AD duration or severity [48], which is consistent with Aβ imaging data of little changes in Aβ accumulation in clinical AD [49] and may suggest that amyloid pathology occurs very early in course of the disease but may have stabilized by the clinical manifestations of DAT.

Increased levels of CSF tau may indicate neuronal injury from multiple causes and were seen in AD patients [41, 45, 48, 50–52] as well as in frontotemporal dementia, stroke and Creutzfeldt-Jacob disease [51]. In preclinical AD, CSF tau levels are correlated with the amount of Aβ deposition [43]. Higher concentrations of CSF tau are associated with greater cognitive impairment in preclinical and clinical AD [53]. In AD, tau undergoes abnormal hyperphosphorylation and phosphorylated tau (p-tau) may offer equivalent if not better diagnostic utility for AD than total tau. Various phosphorylated epitopes may be effective in differentiating AD patients from controls [54], and p-tau231 appears to provide diagnostic specificity for AD and to improve the differentiation between AD and frontotemporal dementia [55], while p-tau181 helps the differentiation between AD and dementia with Lewy bodies [54].

The ratios of CSF tau/Aβ42 and p-tau/Aβ42 in CN individuals strongly predict progression to clinical state of AD. Over 3–4 years of follow-up, 70% of individuals with elevated tau/Aβ42 ratios became clinically positive in one study [52], and another study demonstrated

that all individuals who converted to mild cognitive impairment had elevated tau/Aβ42 ratios [56].

Aβ tracers

With the development of positron emission tomography (PET) radiotracers with high in vivo binding to Aβ plaques it is now possible to quantify pathological changes in the human brain that were previously restricted to post-mortem studies. Ideally, Aβ tracers should: 1) effectively image brain Aβ deposition; 2) have good reproducibility across many subjects and clinical settings; and 3) be widely accessible and appropriate for the particular task [57]. Only a few current tracers satisfy these requirements; however, new tracers for Aβ imaging are under development.

As the comparative review of chemistry of Aβ–specific ^{11}C and ^{18}F PET radiopharmaceuticals has been recently provided by others [58, 59], we will present very briefly characteristics of known radiotracers and focus our discussion on the existing PET imaging data in preclinical AD. [^{18}F]FDDNP [60] was the first reported PET-tracer to image AD pathology *in vivo*. A higher retention of the compound was demonstrated in hippocampus, amygdala and enthorhinal cortex of individuals with symptomatic AD compared with CN persons [61]. However, [^{18}F]FDDNP has relatively high non-specific binding although it may also bind to tau protein [62–64]. The stilbene 4-N-[^{11}C-methyl]amino-4'-hydroxystilbene ([^{11}C] SB-13) has been proposed as a compound with high affinity for Aβ, high initial brain uptake and relatively rapid washout from normal rat brain after an intravenous injection, however it has relatively higher uptake in healthy individuals [65, 66].

Recently, several ^{18}F-labeled tracers in addition to FDDNP were designed and are currently under study including flobetapir ([^{18}F]AV-45), flutemetamol ([^{18}F]GE067), florbetaben ([^{18}F] BAY94–9172) [63, 67–69]. [^{18}F] BAY94–9172 demonstrated neocortical binding in AD patients which was greater in precuneus/posterior cingulate and frontal cortex than in lateral temporal and parietal cortex, with relative sparing of occipital, sensorimotor and medial temporal cortex. At 90–120 min after injction, higher neocortical SUVR was observed in AD patients compared to healthy controls or patients with frontotemporal lobar degeneration. Visual interpretation was 100% sensitive and 90% specific for detection of AD [67]. It has been suggested that further validation of [^{18}F] BAY94–9172 is required in order to evaluate better the kinetics and metabolism of the tracer and determine appropriate quantification method [67].

[^{18}F] AV-45 has high binding affinity, as demonstrated by in vitro binding studies using AD brain homogenates; high selective Aβ plaque labeling, as demonstrated by in vitro autoradiography using postmortem AD brain sections; and excellent brain penetration and rapid kinetics in healthy mice and nonhuman primates [70–72]. The radiochemistry of [^{18}F] AV-45 has been optimized to make this procedure simpler and more convenient and suitable for routine production and distribution of this radiopharmaceutical [71, 72]. In humans, [^{18}F] AV-45 is well tolerated and it shows significant discrimination between AD patients and healthy controls [73]. It is rapidly cleared from circulation, and maximum uptake occurs approximately 30 minutes after injection and remains essentially unchanged for the subsequent 60 minutes [73], providing enough time to obtain a 10-min image. The dosimetry of [^{18}F] AV-45 is suitable for clinical and research applications including longitudinal studies of Aβ accumulation [74]. No evidence of elevated Aβ deposition with [^{18}F] AV-45 was demonstrated in CN individuals within the age range of 18 and 50 years, regardless of APOE genotype [75]. [^{18}F] AV-45 imaging in multicenter study was correlated with the presence and density of Aβ at autopsy, and more studies are ongoing to

evaluate this marker in the clinical diagnosis of AD and for the prediction of progression to dementia [75]. Aβ tracers also have been proposed for single photon emission tomography, including ^{123}I-IMPY and ^{125}I aurone derivatives [76–79].

[^{11}C] PIB PET

[^{11}C]PIB currently is the most studied and used tracer for PET imaging of cerebral Aβ pathology *in vivo* [80, 81]. Significantly higher cerebral binding of [^{11}C]PIB has been demonstrated in a specific pattern in the individuals with symptomatic AD patients compared with CN older adults [49, 82–84] (Figure 1). [^{11}C] PIB is selective for fibrillar Aβ with high affinity to a single binding site in homogenates from AD brains [85, 86] and minimal binding to cerebellum. Therefore, standard uptake values, corrected by using the cerebellum as reference region, provide reproducible results with a scanning time of 60–90 min [85]. Methodology and radiation dosimetry for quantitation of [^{11}C] PIB uptake has been documented [87, 88]. [^{11}C] PIB brain uptake may be quantified using distribution volume ratios (DVR) or binding potentials (BP) obtained with the Logan graphic method using the cerebellum as the reference region, or it may be assessed using some standardized uptake value ratio (SUVR), which is analyzed manually or with automatic algorithm and usually represents the ratio of [^{11}C] PIB accumulation in particular cortical region to [^{11}C] PIB retention in the whole brain [84, 89–92]. Recently, an image-derived input function approach was proposed for quantitative assessment of [^{11}C] PIB retention without arterial sampling [93] and other techniques are under development.

Regional analysis is usually provided with manually defined regions of interests (ROIs) using co-registered MR image [84, 85, 94]; and semi-automatic and automatic [95] or voxel-wise (SPM) analysis may also be used [90]. Various ROIs and global means of representative cortical regions are used by different centers. In our university, we define mean cortical binding potential (MCBP) calculated from the mean of the binding potential values in the prefrontal cortex, gyrus rectus, lateral temporal, and precuneus regions [42, 84, 96, 97]. Others use mean cortical DVR averaged from frontal, anterior cingulate, precuneus, lateral temporal, and parietal cortex and striatum [94] or calculate mean DVR from manually drawn orbitofrontal, prefrontal, superior frontal, parietal, lateral temporal, occipital, and anterior and posterior cingulate regions [98]. Average cortical SUVR may also be calculated from area-weighted mean of frontal, superior parietal, lateral temporal, lateral occipital, and anterior and posterior cingulate regions [95]. Although there is some consensus between various centers regarding these regions, variations in ROIs and protocols for manually drawn regions make cross-center comparisons difficult. A standardized, automated approach with full, accurate segmentation of the brain is still needed in the field. A promising approach is the use of the FreeSurfer (http://surfer.nmr.mgh.harvard.edu), a set of automated tools for reconstruction of the brain's cortical surface from structural MRI data, to create multiple standard regions of interests and facilitate the quantitative regional analysis of PET images. FreeSurfer automatically segments and parcellates T1-weighted brain MR images [99–101] and create distinct regions in cortical and subcortical gray matter, which then can be applied to co-rewho had [^{11}C] PIB scanning prior to shunt placement [110]. Excellent agreement existed between levels of [^{11}C] PIB PET uptake and Aβ quantitation in the post-mortem regions [108]. The biopsy study showed high correlation with Pearson r = 0.85 and very good agreement in 9 of 10 biopsies [110]. However, in one biopsy there was evidence of Aβ by histology but when the [^{11}C] PIB PET scan was done (after a period of 20 months) there was no elevated [^{11}C] PIB uptake in the brain region. There is no clear explanation for this apparent "false-negative" [^{11}C] PIB PET scan, in view of the excellent correlation of [^{11}C] PIB and Aβ in the other subjects.

[^{11}C] PIB has been shown to bind specifically to Aβ-40 and Aβ-42 synthetic fibrils and insoluble Aβ plaques containing Aβ-42 and Aβ-40 found in AD brain [108, 111]. In contrast, [^{11}C] PIB does not bind appreciably to soluble Aβ and probably does not bind to oligomeric forms of Aβ nor to nonfibrillar plaques until they reach some critical size (yet to be determined). [^{11}C] PIB binding requires an extended Aβ pleated sheet structure found in Aβ fibrils and plaques in order to bind with high affinity. The binding of the tracer [^{11}C]PIB to NFTs has been previously evaluated and is regarded as negligible [112, 113]. However, Johnson et al. [114] demonstrated substantially increased [^{11}C]PIB binding in the occipital cortex of patients with cerebral amyloid angiopathy. ^{18}F-labeled PIB analogues have been synthesized recently and are under experimental evaluations now [115, 116].

Aβ imaging in preclinical AD

The concept of preclinical AD postulates that AD lesions accumulate in the brain for years prior to appearance of cognitive deficits or symptoms of dementia [36]. Preclinical AD assumes that AD pathology in CN individuals ultimately culminates in progressive neuronal deterioration that results in the clinical manifestations of DAT, although the time to DAT may differ depending on reserve capacities of an individual [117–119]. It is possible that some individuals with presumptive preclinical AD may never develop DAT, no matter how long they live.

Postmortem morphometric analysis of lesion densities in individuals age 54 to 89 years of age who were CN in life or who had very mild DAT or advanced DAT found that large densities of senile plaques and Aβ immunohistochemistry were present in the neocortex in all demented cases and in 31% of CN individuals, while NFTs were restricted in the CN individuals to the parahippocampal gyrus and hippocampal field CA1 [120]. These observations were extended in subsequent reports [4, 121, 122], concluding that the cerebral deposition of amyloid in the form of Aβ plaques appears to accelerate an age-related tauopathy and that the AD disease process begins well before clinical detection of dementia. Seven of 26 CN individuals older than age 75 had extensively distributed neocortical diffuse and neuritic senile plaques in densities sufficient for a neuropathological diagnosis of AD, which was interpreted as a preclinical stage of AD [4].

Current recommendations from the National Institute on Aging and Alzheimer's Association workgroups are that both the underlying pathological and pathophysiological process of AD and clinical symptoms should be best conceptualized as a continuum or a trajectory, and that these processes may evolve in parallel but temporally offset trajectories [39]. According to this concept, three staging categories were defined for preclinical AD research. Stage 1, "the stage of asymptomatic cerebral amyloidosis", implies biomarker evidence of Aβ accumulation with elevated PET tracer retention and/or low CSF Aβ42, but no detectable evidence of additional brain alterations suggestive of neurodegeneration or behavioral impairment. Stage 2, "amyloid positivity + evidence of synaptic dysfunction and/or early neurodegeneration", includes besides amyloid accumulation, presence of one or more markers of downstream neuronal injury related to AD pathology, including elevated CSF tau or phospho-tau, decreased FDG uptake and cortical thinning/atrophy in AD-prone cortical regions. Stage 3, "amyloid positivity + evidence of neurodegeneration + subtle cognitive decline", is characterized, besides evidence of Aβ accumulation and neurodegeneration, by appearance of subtle cognitive decline and approaching the border zone with the proposed clinical criteria for mild cognitive impairment [39].

Imaging and molecular biomarkers for AD now identify *in vivo* correlates of neuropathological AD and may be used as markers of preclinical AD. Abnormally elevated [^{11}C]PIB uptake in what has been considered "healthy aging" has been consistently

demonstrated from very early [^{11}C]PIB studies and it is likely an important *in vivo* pathological hallmark of preclinical AD. In the initial report by Klunk et al. [80], elevated PIB uptake was seen in 1 of the 6 CN older controls. In a subsequent study [84], 4 of the 23 subjects over 65 yrs had elevated PIB uptake. Later Pike et al. [123] identified 22% of the 32 CN controls and Aizenstein et al. [94] reported 21% of 43 clinically unimpaired elderly persons as having Aβ plaques. Higher frequency (30–33%) of elevated [^{11}C]PIB BP in CN adults especially in older individuals are observed in recent studies involving larger cohorts, and these percentages are comparable to age-related frequency of neuropathological AD on postmortem examination of CN adults [96, 124, 125].

The spatial distribution of [^{11}C] PIB uptake in CN older individuals is similar to AD individuals and is elevated in the posterior cingulate, precuneus, gyrus rectus, orbitofrontal, prefrontal and lateral temporal cortex with relatively spared occipital and sensorimotor areas (Figure 2) [80, 84, 94, 123, 126]. The highest [^{11}C] PIB BP of all gray matter regions is noted in the posterior cingulate, precuneus and prefrontal cortex [84, 94, 95, 127]. CN individuals demonstrate similar or lower levels of [^{11}C] PIB uptake compared to mild cognitive impairment and DAT [84, 95].

Autosomal dominant AD attracts increasing attention, because it allows evaluation of Aβ accumulation in young and middle-aged adults with known mutation years or decades before clinical manifestations. [^{11}C] PIB PET studies have revealed evidence of Aβ regional deposition especially in precuneus, posterior cingulate and prefrontal cortex, and in stratum, in carriers, including those who were up to 10 years younger than the age of onset for their family [128– 130].

In longitudinal studies using [^{11}C] PIB as an indicator for Aβ accumulation, no or little increase in tracer uptake was found during 1–3 years of follow-up in individuals with mild cognitive impairment and DAT [82, 131, 132]. These findings indicate that brain Aβ accumulates more rapidly in the early phases of AD and only very slowly in the more advanced stages of the disease. Recent longitudinal [^{11}C] PIB studies demonstrated increase of Aβ accumulation over time in CN individuals with elevated baseline levels of Aβ [95, 98].

Sojkova et al [98] reported longitudinal [^{11}C] PIB DVR data in 14 older individuals with minimal and 10 with elevated initial Aβ accumulation. The group with elevated mean cortical DVR showed significant 2.3% increase in Aβ accumulation compared to baseline, and all 4 individuals with three [^{11}C] PIB studies demonstrated continuous progression, which was linear in 3 cases of 4. Regionally, significant increases in [^{11}C] PIB DVR were observed in the prefrontal, superior frontal, parietal, lateral temporal, occipital, and anterior cingulate cortex, and in the combined group of CN adults the highest annual increase was demonstrated in posterior cingulate cortex. None of these participants met the diagnostic criteria for mild cognitive impairment (MCI), however 4 had CDR 0.5, and they all demonstrated increases over time in global cortical and regional [^{11}C] PIB DVR [98]. The results indicate that overall magnitude of change may be dependent on the duration of follow-up; with smaller changes resulting from shorter follow-up. A low average rate of Aβ growth in a group may be also due to individual variability, as some individuals demonstrate substantial increases in Aβ accumulation over time, while others, especially older individuals, may show no increases or even decreases in [^{11}C] PIB uptake.

Villemagne et al. [95] recently reported significant increases in mean cortical [^{11}C] PIB SUVR after 20-month follow up in DAT but not in mild cognitive impairment or CN individuals. However CN participants demonstrated more substantial increase after 38-month follow-up compared to individuals with mild cognitive impairment and DAT, and

only CN individuals demonstrated significant increase in mean cortical and regional (orbitofrontal and dorsolateral prefrontal cortex) [^{11}C] PIB SUVR between 20 and 38 months of follow-up [95]. Objective cognitive impairment was demonstrated in 5 of 32 CN individuals with elevated baseline [^{11}C] PIB SUVR at 20-month follow-up and in 8 of 10 individuals who reached the 38-month time point. These 8 individuals who demonstrated cognitive impairment had significantly lower memory scores, higher baseline [^{11}C] PIB SUVR, and higher [^{11}C] PIB SUVR increases than those individuals who did not progress. These data suggest initial rise and then plateau in DAT individuals, but continuously progressive Aβ accumulation with clinical worsening in CN individuals with high Aβ burden.

Increasing age and genetic background are the strongest known risk factors for AD. The APOE ε4 allele is the major genetic susceptibility factor for late-onset AD, with an expressing gene dose-dependent risk for the development of DAT at an earlier age of onset [133–135]. Other isoforms of APOE are considered to be neutral (APOE ε3) or even protective (APOE ε2) for AD risk [136, 137]. The increased risk of APOE ε4 for AD may be mediated by disturbances in cerebral Aβ metabolism [138–140]. There is isoform-dependent propensity (ε4 > ε3 > ε2) for Aβ deposition in experimental animals [141, 142], and in humans [96]. APOE ε4 carriers have increased cerebral amyloid deposition compared to non-carriers [143–145]. The role of APOE ε4 in promoting AD appears to be directly related to its effect on AD pathology, because its association with clinically diagnosed DAT is non-significant after controlling for the densities of senile plaques and neurofibrillary tangles in autopsied individuals [146]. Consistent with this premise, an APOE genotype effect on Aβ load has been demonstrated in individuals with moderate DAT [147] and in CN individuals [96, 124, 126, 148, 149]. In a large cohort of CN individuals, APOE ε4 demonstrated a powerful dose-dependent effect on cerebral Aβ deposition as measured with [^{11}C] PIB and on CSF levels of Aβ42, but not tau or ptau$_{181}$ levels [96]. These data suggest that Aβ abnormalities, but not tau abnormalities, initiate the pathological cascade of preclinical AD.

Increasing evidence suggests that preclinical AD is not benign but eventually produces sufficient synaptic and neuronal damage to cause cognitive decline and other symptoms of AD [36, 150]. Reduced levels of CSF Aβ42 in CN older adults are associated with whole brain atrophy [151], and with hypometabolism in the medial temporal lobe [152]. CN older individuals with elevated [^{11}C]PIB binding levels also demonstrate multiregional brain atrophy [153–155], cerebral cortical thinning [156], aberrant default network activity and functional MRI connectivity deficits similar to AD [157–160], decreased task-induced fMRI deactivation in the default network regions [161], lower performance on a demanding test of associative memory retrieval [162], episodic memory deficits [123, 163], as well as longitudinal cognitive decline [153]. CN individuals with elevated MCBP are at significantly greater risk of developing the symptomatic stages of AD than individuals with less or no [^{11}C]PIB retention [150]. Moreover, this [^{11}C]PIB predictive effect is restricted to symptomatic AD and does not encompass non-DAT causes of mild dementia [150]. Villemagne et al [95] reported that there is a 16% risk of developing mild cognitive impairment or DAT over 20 months and 25% risk by 3 years in CN individuals with high [^{11}C]PIB retention. Higher educational attainment [119] or socioeconomic status [164] may permit individuals with preclinical AD, as ascertained by [^{11}C]PIB, to better tolerate AD pathology without obvious cognitive deterioration, suggesting that they have a greater reserve against the clinical expression of AD [165].

Recently it has been suggested that certain lifestyle practices such as physical exercise could potentially deter or slow disease progression [166]. Physical exercise has been recognized as preserving not only cardiovascular but also brain and cognitive health in older adults [167]. It has been recommended by Alzheimer's Association to clinicians as a way to maintain

cognitive functioning in AD and enhance a patient's quality of life, and studies suggested that exercise may reduce risk of cognitive decline and dementia [168, 169], and may have beneficial effects on AD-related pathology [170–173] including Aβ deposition as measured with [^{11}C]PIB PET [166].

Hinrichs et al. [97] recently studied the heritability of Aβ deposition as expressed by MCBP using [^{11}C]PIB PET and demonstrated that MCBP is a genetic trait with significant unique variability and that other Aβ related traits such as cerebrospinal fluid Aβ42 or APOE ε4 genotype do not fully explain the variance in MCBP. The predictive accuracy of MCBP alone for identification of symptomatic AD is quite high but it can be improved substantially when MCBP is used together with other factors including education, normalized whole brain volume, physical health rating, gender and use of medications that may interfere with cognition [174].

Research and therapeutic directions in preclinical AD

Further directions include the need in carefully organized longitudinal studies with multiple repeated imaging and other diagnostic assessments. While substantial data has been collected in AD using anatomical, metabolic and molecular imaging techniques, most data is cross-sectional and those few longitudinal studies are limited in number of participants and do not have enough temporal resolution to characterize the onset and growth of Aβ plaques. More longitudinal data is needed to demonstrate whether Aβ plaque levels stabilize very quickly after appearing, or alternatively, there is a slow and steady accumulation of Aβ plaques over a prolonged period of time. Longitudinal studies are critical also for the development of a reliable tool for documentation of the transfer from healthy aging to preclinical AD. This conversion may be determined by some threshold level of global Aβ deposition, but this arbitrarily approach should be evaluated in larger samples and validated by clinicopathological correlations to better characterize the incidence of preclinical AD. Time of conversion is very likely the most important period for the selection for preventive treatment trials.

It should be noted that careful design of clinical trials to test disease-modifying agents is critical, with largely enough sample sizes and optimal parameters chosen to adequately power these trials. Government and industry officials as well as academia researchers should consider the optimum use of the clinical trials design for disease-modifying agents on AD in their effort to search for the treatments with the potential to modify the underlying pathophysiology of AD [175]. Starting as early as possible before the appearance of cognitive symptoms, the preclinical stage of AD should be a critical strategy for preventive therapies aimed on decreasing production, increasing clearance, decreasing aggregation and removing aggregates of Aβ. It is likely that the metabolic changes in Aβ-prone regions may actually begin at the same time as observed plaque development in CN subjects, suggesting neuronal dysfunction is a very early part of the pathological cascade and there would be an incentive to begin treatment early as well.

Combining the efforts of multiple institutions and creating joint databases of clinical and imaging information is of critical importance for successful research and clinical efforts. A good example is the Alzheimer's Disease Neuroimaging Initiative (ADNI), a multicenter research project that studies changes of cognition, brain structure and function, and biomarkers in elderly healthy individuals, participants with mild cognitive impairment and persons with symptomatic AD with a major goal to determine and validate MRI, PET and CSF/blood biomarkers as predictors and outcomes for use in clinical trials of AD treatments[176–183].

Another good example is related to autosomal dominant AD, which, representing less than 1% of all AD cases, may nevertheless be considered as one of the best populations for early preventive trials because it allows treating asymptomatic young adults, not affected by other brain diseases seen commonly in older individuals, and years or decades before clinical onset [184]. Due to the geographically dispersed nature of autosomal dominant families and relative rarity of the disease, an international network of research centers, known as Dominantly Inherited Alzheimer's Network (DIAN) has been established to enable adequately powered longitudinal multicenter studies and clinical trials in this unique and highly informative population [184].

Highlights

Recent advances PET imaging now make it possible to detect AD amyloid pathology in the preclinical stagse of the disease, in cognitively normal (CN) individuals. This review focuses on amyloid PET imaging for AD, including the biological basis of the imaging agents, data

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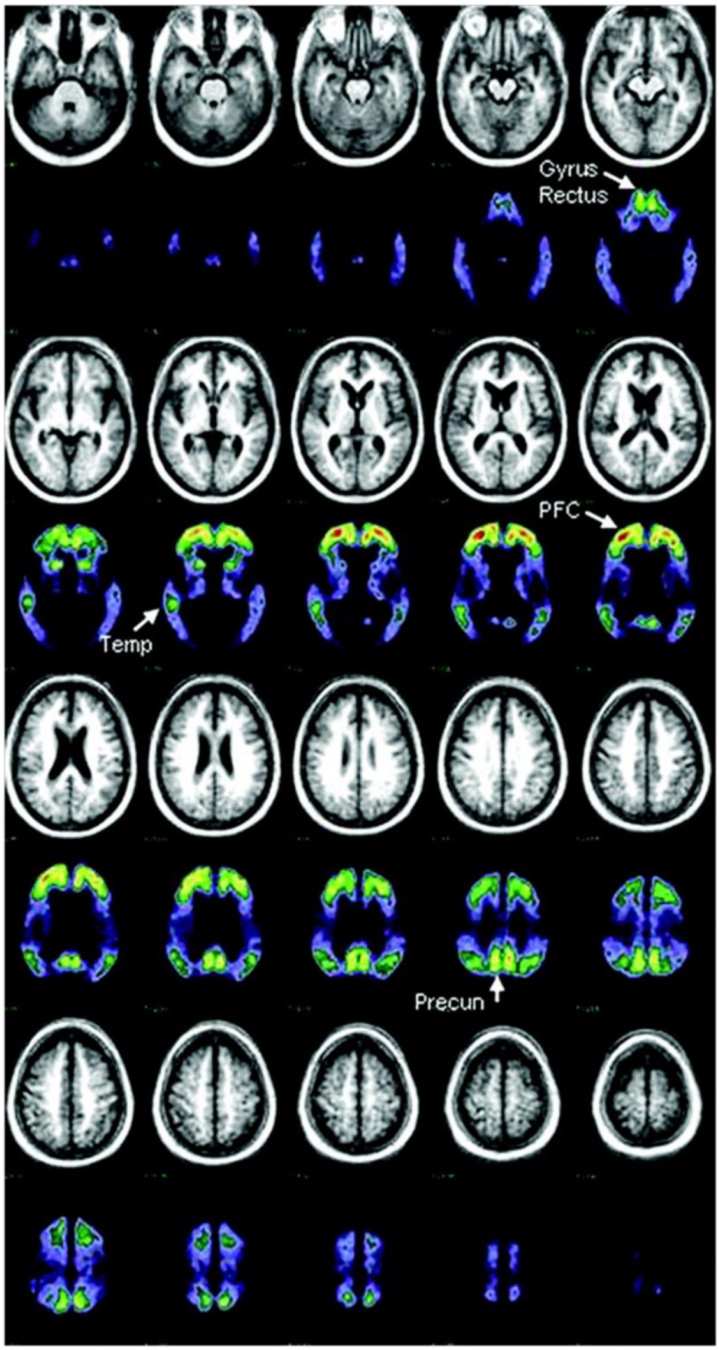

Figure 1.
Mean MRI and PET [^{11}C]PIB distribution in a standard atlas coordinate system from 10 subjects with dementia of the Alzheimer type. PET data represent [^{11}C]PIB activity in the late (30 to 60 minutes after injection) distribution and has been normalized to standardize display and increase contrast. Brain areas used to detect raised [^{11}C] PIB uptake in nondemented subjects are indicated with arrows. PFC = prefrontal cortex; Temp = temporal cortex; Precun = precuneus region. Reproduced with permission from [84].

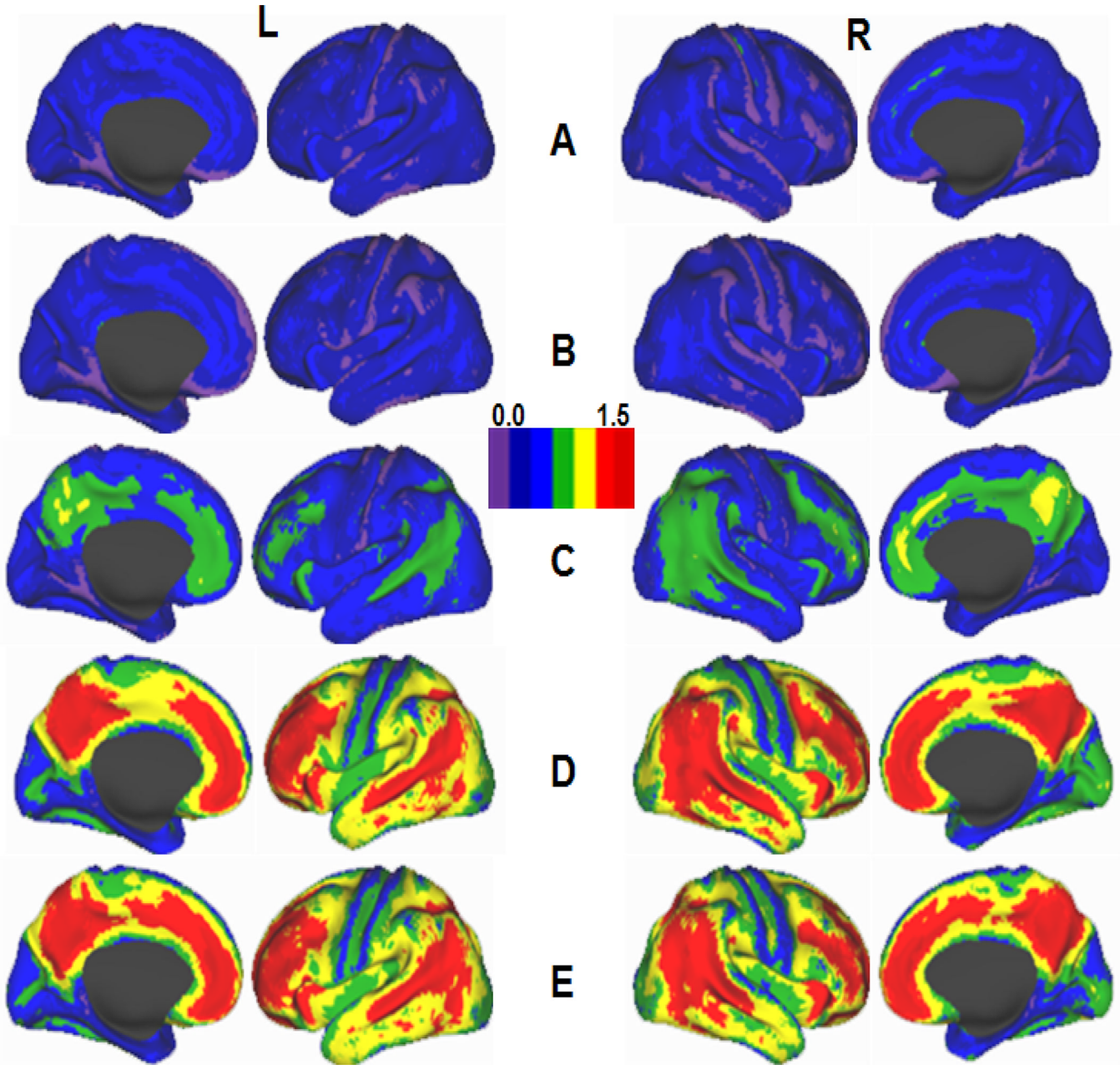

Figure 2.

Schematic maps showing [^{11}C] PIB BP distribution on lateral and medial cortical surfaces of the left (**L**) and right (**R**) hemispheres of the human brain. **A**, Healthy young (< 50 y. o) adults; **B–D**, Cognitively normal older (> 50 y. o.) adults with low (**B**), moderate (**C**) and high (**D**) Aβ deposition; **E**, Individuals with dementia of Alzheimer's type (modified from Vlassenko et al. 2010 with permission).