Dementia is characterized by a progressive loss of mental function altering the normal activities of daily living, affecting principally memory and executive functions as well as leading to personality changes. The progressive nature of neurodegeneration suggests an age-dependent process that ultimately leads to synaptic failure and neuronal damage in cortical areas of the brain essential for memory and higher mental functions [1]. In the absence of specific biological markers, direct pathologic examination of brain tissue remains as the only definitive method for establishing a diagnosis [2, 3].

Currently, the clinical diagnosis of dementia is based on progressive impairment of memory, decline in at least one other cognitive domain, changes in personality, and the exclusion of other diseases [4]. A period of up to five years of prodromal decline in cognition, known as Mild Cognitive Impairment (MCI), usually precedes the formal diagnosis of dementia [5, 6]. About 40-60% of carefully characterized subjects with MCI will subsequently progress to meet criteria for Alzheimer’s disease (AD) over a three to four year period [7].

Alzheimer’s disease represents about 60% of the cases of dementia in the elderly. AD is an irreversible, progressive neurodegenerative disorder clinically characterized by memory loss, cognitive and functional decline [8]. It leads invariably to death, usually within seven to ten years after diagnosis. AD not only has devastating effects on the sufferers and their caregivers, but it also has a tremendous socioeconomic impact on families and the health system, a burden that will only increase in the upcoming years [9, 10].

While AD is the most common cause of dementia in the elderly, post mortem studies have found dementia with Lewy bodies (DLB) to account for 20% of cases [11]. Although the pathological hallmark of DLB is the finding of cortical Lewy bodies, the majority of cases also show extensive cortical amyloid deposition [11]. Parkinson’s disease (PD) is one of the most common neurological disorders, affecting approximately 1% of individuals older than 60 years [12].

The major neuropathological findings are a loss of pigmented dopaminergic neurons in the substantia nigra and the presence of Lewy bodies. However, cortical Aβ may be present when PD patients develop dementia along with Lewy bodies in the neocortex. This suggests a central role for Aβ in several types of dementia.

Frontotemporal lobe degeneration FTLD accounts for 20% of cases of dementia in post mortem studies [13]. Neuropathologically, there is atrophy of frontal and temporal lobes, severe neuronal loss, gray and white matter gliosis, and superficial laminar spongiosis, with absence of amyloid aggregates. In many cases, there is accumulation of insoluble tau or TDP43 within neurons and glia [14].

Molecular imaging thus possesses greater potential for accurate, early and differential diagnosis as well as monitoring of disease progression and therapeutic effects [16]. These techniques have been extensively used to examine cerebral glucose metabolism, neurotransmitter and neuroreceptor systems along with the enzymes associated with their synthesis and metabolism, neuroinflammatory processes as well as specific markers of disease.

Glucose metabolism

Fluorodeoxyglucose (FDG) PET, mainly used for the differential diagnosis of dementia, is the neuroimaging technique that yields the highest prognostic value, providing a diagnosis of symptomatic AD two or more years before the full dementia picture is manifested [17, 18]. Several studies have evaluated regional cerebral glucose metabolism with FDG PET.
A typical pattern of reduced temporoparietal FDG uptake with sparing of the basal ganglia, thalamus, cerebellum, and primary sensorimotor cortex is typical of AD [19]. Patients with DBL present with hypometabolism in the occipital and temporoparietal areas, with relative preservation of the posterior cingulate gyrus while FTLD patients present with reduced frontal and temporal metabolism (Figure 1).

In a multicenter study, the prognostic value of FDG-PET showed a high degree of sensitivity (93%) and moderate specificity (73%) for prediction of progressive dementia [18]. Posterior cingulate and temporoparietal hypometabolism was observed in MCI patients when compared to controls. Progression of some of these patients to probable AD showed an additional bilateral hypometabolism in prefrontal areas, with further reductions in the posterior cingulate and parietal cortex. No such changes were observed in the MCI group that remained stable [23].

**Neurotransmitter systems**

Molecular imaging techniques can also assess neurotransmitter systems in vivo. The evaluation of neurotransmitter functions in the brain is helpful for the determination and monitoring of treatment protocols, prediction of disease progression, as well as for the early diagnosis of dementia. Though the focus of neuroreceptor studies in AD has been the study of nicotinic acetylcholine receptors (nAChRs), several other neurotransmitter/neuroreceptor systems were also evaluated in dementia [24-29].

In a variety of central processes, nAChRs have been implicated, such as memory and cognition [30]. Abnormally low densities of nAChRs have been measured in vitro in autopsy brain tissue of AD patients. There is great interest in developing radiotracers to image nAChRs noninvasively in order to evaluate receptor impairments, even at a presymptomatic stage of AD, as well as monitoring drug treatment outcomes [31].

**Molecular imaging can assess neurotransmitter systems in vivo.**

Typical cerebral distribution of nAChR in elderly control subjects is shown in Figure 2. PET studies revealed a reduced uptake and binding of $^{11}$C-nicotine in the temporal and frontal cortices of AD patients [32]. However, studies using 2-$^{18}$F fluoro-A-85380 found no evidence of in vivo nAChR loss in early AD despite significant cognitive impairment [33]. Functional imaging of cholinergic neurotransmission is a useful strategy for the determination of the treatment protocol of demented patients.

Treatment with cholinergic drugs, such as Tacrine and Aricept (donepezil), in AD patients could lead to recovery of the nAChRs in the brain, as visualized by PET. Tacrine treatment increased cerebral blood flow, cerebral glucose utilization, and uptake of $^{11}$C-nicotine to the brain paralleled by improved neuropsychological performance. Changes in nicotinic receptors and blood flow were observed after three weeks of treatment while changes in glucose metabolism were measured after three months of treatment [34, 35].

Functional studies have also evaluated enzymes directly involved in the hydrolysis of acetylcholine (ACh). PET studies using $^{[11]C}$ MP4A and $^{[11]C}$ PMP have shown markedly reduced acetylcholinesterase (AChE) activity in AD [36] while studies with $^{[11]C}$ donepezil revealed lower binding in AD patients, reductions that correlated with dementia severity [37]. These tracers have also been used to assess AChE occupancy by orally administered AChE inhibitors [38].

Dopaminergic neuronal loss in DBL and PD with dementia can be assessed by examining dopaminergic terminals with PET or SPECT, using ligands specific for the dopamine transporter, such as [23]I β CIT, [123]I FPCIT or [11C]-WIN [39], or for the vesicular monoamine transporter type 2 (VMAT2) with tracers such as $^{[11]C}$-DTBZ or $^{[18]}$F-AV133 (Figure 3) [40]. Evaluation of dopamine synthesis by $^{[18]}$F FDOPA PET also showed a marked reduction in striatal accumulation in DBL patients [41], suggesting that the assessment of dopaminergic terminals would help in the differential diagnosis of dementia.

**Neuroinflammation**

Microglial activation is a useful indicator of neuroinflammation and can be used to assess anti-inflammatory therapies. Activated microglia has been examined using $^{[11]C}$-PK11195, a tracer for the peripheral benzodiazepine receptor (PBR). Studies with $^{[11]C}$-PK11195 PET demonstrated
a significant increase in microglial activation in AD brains, and while a correlation with dementia severity has been shown [42], the increase in microglial activation is not associated with Aβ deposition [43]. Efforts are focused on developing PBR radiotracers that are more sensitive [44].

### Amyloid imaging

Neurofibrillary tangles (NFT) and Aβ senile plaques are the neuropathological hallmarks of AD. Whilst NFTs are intraneuronal bundles of paired helical filaments mainly composed of the aggregates of an abnormally phosphorylated form of tau protein [45], neuritic plaques consist of dense extracellular aggregates of amyloid β -peptide (Aβ) [46], surrounded by reactive gliosis and dystrophic neurites. Aβ is a 4 kDa 39–43 amino acid metalloprotein derived from the proteolytic cleavage of the amyloid precursor protein (APP), by β and γ-secretases [47].

To date, all evidential analysis strongly supports the notion that an imbalance between the production and the removal of Aβ, leading to its progressive accumulation, is central to AD pathogenesis [48]. While at this point there is no cure for AD, a deeper understanding of the molecular mechanisms of Aβ formation, degradation, and neurotoxicity is being translated into new therapeutic and molecular imaging approaches [8, 49].

Amyloid imaging is providing quantitative information on Aβ burden in vivo, leading to new insights into Aβ deposition in the brain and facilitating research of dementing diseases [50]. The most successful and widely used of the currently available amyloid tracers, 11C-PiB has been shown to possess high affinity for fibrillar Aβ. This allows the examination of a large spectrum of diseases where Aβ may play a role, as well as in other neurodegenerative diseases associated with misfolded proteins such as prion diseases, synucleopathies or taupathies (Figure 4) [51-53].

On visual inspection cortical retention of 11C-PiB, regardless of disease severity, is markedly elevated in AD [50]. The regional brain distribution is similar in both AD and DLB being highest in frontal, cingulate, precuneus, striatum, parietal, and lateral temporal cortex (Figure 4). The regional retention of 11C-PiB reflects the regional density of Aβ plaques, as reported at autopsy [54] as when measured by quantification of immunohistochemical staining of brain slices, with a higher plaque density in the frontal cortex than in hippocampus, consistent with previous neuropathological and PiB PET reports [50, 55].

Both quantitative and visual assessment of 11C-PiB-PET images presents a pattern of 11C-PiB retention that seems to replicate the sequence of Aβ deposition found at autopsy [56]. With initial deposition being found in the orbitofrontal cortex and gyrus rectus, followed by the cingulate gyrus and precuneus, the remaining prefrontal cortex and lateral...
Approximately 30% of apparently healthy older people, and 50-60% of people with mild cognitive impairment, present with cortical 11C-PiB retention (Figure 4). In these groups, Aβ burden does correlate with episodic memory and rate of memory decline [59]. These observations suggest that Aβ deposition is not part of normal ageing, supporting the hypothesis that Aβ deposition occurs well before the onset of symptoms and is likely to represent preclinical AD [50, 59]. Further longitudinal observations, coupled with different disease-specific tracers and biomarkers are required not only to confirm this hypothesis, but also to better elucidate the role of Aβ deposition in the course of AD.

Development of promising new Aβ imaging ligands labeled with isotopes having longer radioactive half-lives and acceptable radiation exposure, such as the case of 18F-BAY94-9172 [60] (Figure 5), will permit widespread application of this technique. They will also provide the accurate, reliable, and reproducible quantitative statements of Aβ burden, essential for therapeutic trial recruitment and for the evaluation of disease-specific treatments directed at removing Aβ.

As new treatments in clinical trials are aimed at preventing or slowing AD progression, either by preventing Aβ generation or deposition, or increasing the clearance of Aβ, the role of imaging and quantifying Aβ burden in vivo is becoming increasingly crucial, being acknowledged as part of newly proposed diagnostic criteria [61]. Although these treatments are aimed at AD, amyloid imaging findings suggest that they may have value in other dementias such as DLB, where Aβ deposition is present.

**Conclusion**

Most dementias are characterized by a progressive decline in cognitive function, having a devastating effect on both the sufferer and their caregivers, inflicting a tremendous socioeconomic impact not only on families but also on the public health system. As a common risk factor for many neurodegenerative diseases is age, the increasing age of the population in developed countries suggests that if unchecked, these disorders will become increasingly prevalent and burdensome to our societies.

The clinical diagnosis is typically based on progressive cognitive impairments whilst excluding other diseases. Clinical diagnosis of sporadic disease is however challenging, often presenting mild and non-specific symptoms attributable to diverse and overlapping pathology presenting...
similar phenotypes. In most cases, confirmation of diagnosis still relies on autopsy.

The neurodegenerative process usually begins decades before symptoms are evident, making early identification based on structural neuroimaging extremely difficult. This in turn precludes early intervention with disease-modifying medications during the presymptomatic period, which by arresting neuronal loss would presumably achieve the maximum benefits of such therapies.

Therefore, a change in the diagnostic paradigm is needed where diagnosis moves away from identification of signs and symptoms of neuronal failure, indicating that central compensatory mechanisms have been exhausted and extensive synaptic and neuronal damage is present, to the non-invasive detection of specific biomarkers for particular traits underlying the pathological process [62].

Given these disorders’ complexity and sometimes overlapping characteristics, and despite recent advances in molecular neurosciences, it is unlikely that a single biomarker will be able to provide the diagnostic certainty required for the early detection of neurodegenerative diseases like AD. Especially those biomarkers needed to identify the at-risk individuals before the development of the typical phenotype.

Consequently, a multimodality approach combining biochemical and neuroimaging methods is needed [63]. Multitracer studies such as the ones shown in Figure 6 can explore different molecular processes increasing the specificity of the diagnosis while helping select and customize treatment to potentially prevent or delay functional and irreversible cognitive loss.

Because new treatment strategies to prevent or slow disease progression through early-intervention are being developed and implemented there is an urgent need for early disease recognition. That is reflected in the necessity of developing sensitive and specific biomarkers, specific for a particular trait or traits underlying the pathological process, as adjuncts to clinical and neuropsychological tests. Molecular imaging might be able to address some of these important issues.

Dementia is a progressive journey to the end of the night. Maybe molecular imaging can assist us to get closer to the threshold of a new dawn, help us find a way out of the labyrinth, turning the whole journey to the end of the night, into a journey into the day.

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References


