Neuroimaging as a marker of the onset and progression of Alzheimer’s disease

Jose C. Masdeu a,d,*, Jose L. Zubieta b, Javier Arbizu c

a Department of Neurology and Neurosurgery, Pamplona, Spain
b Department of Radiology, Pamplona, Spain
c Department of Nuclear Medicine, University of Navarra Medical School, Pamplona, Spain
d Neuroscience Department, Clínica Universitaria de Navarra and Center for Applied Medical Research, University of Navarra, Pamplona, Spain

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Abstract

Several neuroimaging techniques are promising tools as early markers of brain pathology in Alzheimer’s disease (AD). On structural MRI, atrophy of the entorhinal cortex is present already in mild cognitive impairment (MCI). In the autosomal dominant forms of AD, the rate of atrophy of medial temporal structures separates affected from control persons even 3 years before the clinical onset of cognitive impairment. The elevated annual rate of brain atrophy offers a surrogate tool for the evaluation of newer therapies using smaller samples, thereby saving time and resources. On functional MRI, activation paradigms activate a larger area of parieto-temporal association cortex in persons at higher risk for AD, whereas the entorhinal cortex activation is lesser in MCI. Similar findings have been detected with activation procedures and water (H215O) PET. Regional metabolism in the entorhinal cortex, studied with FDG PET, seems to predict normal elderly who will deteriorate to MCI or AD. SPECT shows decreased regional perfusion in limbic areas, both in MCI and AD, but with a lower likelihood ratio than PET. Newer PET compounds allow for the determination in AD of microglial activation, regional deposition of amyloid and the evaluation of enzymatic activity in the brain of AD patients.

Keywords: Alzheimer; MRI; fMRI; PET; SPECT; Functional brain imaging; Neuroimaging; Molecular brain imaging; Early marker

1. Introduction

By the time Alzheimer’s disease (AD) or even mild cognitive impairment (MCI) are clinically detectable, an important neuronal loss has already taken place [1]. As the search quickens for effective ways to halt the clinical development of the disease in those predisposed to it, early diagnosis or even presymptomatic diagnosis becomes crucial [2]. Neuroimaging is one the methods being actively studied as a way of predicting the evolution of Alzheimer’s disease in patients with MCI and even in people at the presymptomatic stage. Neuroimaging is also being explored as a marker of disease progression and therefore as a surrogate marker of the effectiveness of new therapies. It is possible that neuroimaging could be a better marker than neuropsychological rating scales, allowing for smaller sample sizes to test new therapies [3–6].

Here we will review the contribution of several imaging modalities to the prediction of who will develop AD among patients with MCI or even in still healthy populations. In order to orient the reader, we will first review the characteristic findings of early AD in the most frequently used imaging modalities. As would be expected, some of these findings are also present at even earlier stages of the disease.
2. Imaging findings in AD

2.1. Structural magnetic resonance imaging

2.1.1. Cross-sectional studies

From the mid-1980s we know that measurements of medial temporal atrophy are most sensitive and specific to detect early AD changes on structural brain imaging [7,8]. These earlier studies were later confirmed by discriminant analysis [9]. The finding of important neuronal loss in entorhinal cortex in early AD or MCI prompted the study of this structure on neuroimaging [1]. In one study, when combined with measurements of the banks of the superior temporal and anterior cingulate sulci, entorhinal cortex volume separated normal elderly from those with mild AD with an accuracy of 100% [10]. A simplification of this method also provides a good discrimination [11]. The extent of the entorhinal and superior temporal cortex can be measured with any graphic program that allows for the measurement of an area of interest (Fig. 1). In order to correct for individual variability, the area obtained from the previous measurements is divided by the product of the axial, transverse and anterior–posterior axes of the brain being studied (Fig. 2). It must be noted that manual outlining of the entorhinal cortex, even when assisted by a graphic program, has not discriminated as accurately in other studies [12,13]. A fully automated method is voxel-based morphometry, which uses Statistical Parametric Mapping [14–16]. Because the individual brains have to be standardized to a template, they have to be slightly deformed, introducing a potential source of error [14]. On the other hand this method is attractive because it prevents operator errors and allows for the comparison across individuals and laboratories of all the brain voxels, not just a few predetermined regions of interest [17].

Structural MRI has also been used to improve the yield of other markers of AD. For instance, the concentration of the tau protein in CSF of MCI patients does not change over time. However, there is a significant increase in hiperfosforilated tau 231 when the total amount in CSF is calculated on the basis of the ventricular size [18].

2.1.2. Longitudinal studies

The annual rate of volume change in entorhinal cortex distinguishes AD from controls with greater sensitivity and specificity than one-time measurements [12]. Whereas the annual volume loss in normal aging is less than 1%, rates as high as 4% occur in early AD [19]. The annual percentage of progression in regional atrophy can be calculated with semiautomated methods [19,20]. An important application of longitudinal structural MRI is as a surrogate marker of disease progression in patients with MCI or AD, thus facilitating the evaluation of new therapies. For instance, in a study of a new muscarinic agonist with a sample size of 192 patients and a follow-up of 1 year, disease progression was better gauged in 99% of the patients with measurements of hippocampal atrophy than with cognitive or behavioral testing ($p < 0.001$) [5]. Using neuroimaging markers would allow for a marked reduction of sample size. In that study, the estimated number of subjects per arm required to detect a 50% reduction in the rate of decline over 1 year were as follows: AD Assessment Scale—cognitive subscale, 320; Mini-Mental Status Examination, 241; hippocampal volume, 21; and temporal horn volume, 54 [5]. The medial temporal region is the first one to be affected in MCI and as the disease progresses, posterior cingulate gyrus and temporo-parietal association cortex are involved [17,19].

2.2. Regional cerebral metabolism studied with PET

Regional cerebral metabolism studies with PET have used $^{18}$F-2-deoxy-2-fluoro-D-glucose (FDG) as a metabolic marker [21–24]. In MCI, the medial temporal region has decreased metabolism [25,26]. The most typical pattern found in early AD is decreased metabolism bilaterally in the parieto-temporal association cortex and cingulate gyrus (Fig. 3). This pattern corresponds to the degree of neuropathologic changes in early AD, more prominent in the medial temporal region, cingulate cortex, and in the parieto-temporal association cortex [27]. As the disease progresses, frontal association cortex becomes involved, while the paracentral cortex (primary motor-sensory areas) remains preserved. The specificity and sensitivity of these findings.

Fig. 1. Coronal MRI at the level of the mammillary bodies. The entorhinal cortex has been outlined in a normal control (A) and a person with mild cognitive impairment (B).
continue to be debated. In a large multicenter study, neuropathological confirmation was obtained in 41 patients with mild AD or MCI (the majority had scores of more than 26 points in the MMSE). In this group brain metabolism correctly indicated the final diagnosis in 89% of the patients (95% CI, 81%–97%), with a sensitivity of 95% (95% CI, 89–100%) and a specificity of 71% (95% CI, 48–95%) [28]. Similar findings have been obtained in studies with fewer patients [29].

2.3. Regional cerebral perfusion

Regional cerebral perfusion studies with SPECT were some of the earliest to distinguish AD patients from controls and are still some of the most widely used in clinical practice [30]. Perfusion with PET has been mainly utilized to study brain activation with different tasks. MRI has recently been added to the cerebral perfusion armamentarium.

2.3.1. Regional cerebral perfusion studied with SPECT

The most commonly used tracers for studying cerebral perfusion with SPECT are Tc-99 m HMPAO (hexamethyl propylamine oxime, Ceretec™), a lipid soluble macrocyclic amine, and Tc-99 m ECD (ethyl cysteinate dimer, Neurorite™). There are many SPECT studies on Alzheimer-type dementias [31–35]. Using a statistical factorial system to compare regional perfusion with SPECT in AD and controls, Johnson could prove that regional perfusion was decreased in the AD group in the following regions: parieto-temporal cortex, hippocampus, anterior and posterior cingulum, and dorsomedial and anterior nucleus of the thalamus. This pattern had a sensitivity of 86% and a specificity of 80% [36]. This and other clinical studies suffer from the lack of neuropathological confirmation of the diagnosis. In a group of 70 patients with dementia and 14 controls, all with autopsy, Jagust et al. [34] compared the diagnostic accuracy of the clinical criteria without and with the help of SPECT. The clinical diagnosis of probable AD was associated with a probability of 84% of a neuropathological diagnosis of AD. A positive SPECT increased the probability of a diagnosis of AD to 92%, while a negative SPECT lowered that figure to 70%. SPECT was most useful when the clinical diagnosis was of possible AD, with a probability of a diagnosis of AD of 67% without SPECT, of 84% with a positive SPECT, and of 52% with a...
negative SPECT [34]. The average score on the Mini-Mental test of the patients in this study was 13, indicating that they were suffering from serious dementia. However, it is interesting that the group in which SPECT supported most the diagnosis was that of possible AD, which logically includes those patients at an earlier stage. Another post-mortem study correlated the SPECT perfusion pattern with the Braak staging [37]. Between the entorhinal and limbic stages, reduced perfusion appeared in the anterior medial temporal lobe, subcallosal area, posterior cingulate cortex, precuneus and possibly the supero-anterior aspects of the cerebellar hemispheres. Then, between the limbic and neocortical stages, large posterior tempo-parietal perfusion defects appear, before finally large frontal lobe perfusion defects with relative sparing of the paracentral cortex are added in the advanced stages [37].

As perfusion SPECT is less expensive and more readily available than FDG PET, a number of studies have compared the two techniques in the same AD patient sample [38–43]. Earlier studies found it even methodologically difficult to compare the studies performed with either technique [38]. The consensus is that PET is slightly more sensitive and specific than SPECT for the diagnosis of mild AD, but it is clearly better for the differential diagnosis of vascular dementia [39,41].

2.3.2. Regional cerebral perfusion studied with PET

Perfusion studies with PET have been carried out mostly to evaluate cerebral activation in relation to specific tasks. For these studies, which we detail below, water marked with radioactive oxygen is used (H$_2$O). However, there are some comparisons of perfusion in early AD and controls [44]. Areas with decreased perfusion also have decreased metabolism. However, there are areas of increased perfusion in early AD, above all in primary cortex and in the dorsolateral frontal region [44].

2.3.3. Regional cerebral perfusion studied with magnetic resonance imaging

Regional cerebral perfusion can be evaluated with several MR techniques. The regional cerebral blood volume (rCBV) can be measured with a quick injection of a paramagnetic contrast that causes a signal decrease in the microvasculature. There are several studies of this type in AD [45,46]. In a clinical study, Bozzao et al. [47] found that a decreased temporoparietal rCBV had a sensitivity of 91% in moderately affected patients with Alzheimer’s disease ($n=18$) and 90% in patients with mild cases ($n=16$). Specificity was 87% in healthy comparison volunteers ($n=15$). Hippocampal cortex perfusion was not as helpful (sensitivity 80% and specificity 65%).

More recently, arterial spin-labeled blood flow MRI has allowed for the performance of perfusion studies without the need to inject contrast. For example, Alsop et al. [48] studied 17 patients with moderate and advanced AD (MMSE of 29 to 6) and detected a decrease in perfusion, compared to controls, in parieto-temporal association cortex and, less profound, in frontal cortex. The medial temporal region could not be studied in enough detail, because the image, obtained using an ecoplanar technique, was degraded at the base of the frontal and temporal lobes. This technique, which provides similar information to that of SPECT, has the advantages that (1) it does not use ionizing radiation, (2) the calculation of regional cerebral flow is easier, and (3) without moving the patient, an MRI can be done at the same time. A structural MRI localizes with greater spatial resolution the blood flow data, and permits the identification of potential ischemic lesions, common in the elderly and which could confound the interpretation of imaging changes in AD. On the other hand, compared to SPECT, this technique has a worse signal to noise ratio, is more sensitive to patient movement and can underestimate blood flow if the transit time of blood from the base of the brain to the tissue is more than 1 s. New perfusion techniques, for instance using pulsed arterial spin labeling, are increasing the efficiency of cerebral MRI in this field [49].

2.4. Regional cerebral activation

2.4.1. Activation studies with PET

PET was the first neuroimaging technique used to obtain cerebral activation studies. These studies are carried out with water marked with radioactive oxygen (H$_2$O), an isotope whose short half-life allows for a temporal resolution of 40 s. With this isotope, cerebral regional blood flow can be measured (regional cerebral blood flow, rCBF). The rCBF increases parallel to the increase in regional oxygen need, which in turn corresponds to an increased synaptic activity in the corresponding region of the brain. For activation studies, a PET is obtained of the relevant zone or of the whole brain in a baseline condition (e.g., the patient is being scanned while resting) and in an activation condition (e.g., the patient trying to memorize two words). The subtraction of rCBF maps obtained in those two situations shows a map of the zones of the brain activated by the task object of the study. The comparison is made with statistical techniques such as Statistical Parametric Mapping (SPM) [50,51].

Several activation studies with H$_2$O PET have shown that in order to carry out the same task, some areas of the cortex are more extensively activated in those with early AD or MCI than in controls [44,52]. This finding has been confirmed by studies of functional MRI [53,54]. Activation studies with PET have been carried out in patients with mild to moderate AD. The group of 7 patients studied by Becker et al. [44] had an average MMSE of 21.7. To accomplish an episodic memory task, they activated similar areas of the cortex as in controls, but more extensively. In agreement with this finding, studying patients with early AD, Woodard et al. [52] showed that when subjects tried to remember the contents of a written text, controlled by reading, only the right lateral frontal region was activated in healthy elderly
people, while in patients with AD similar regions were activated but in both hemispheres. These findings have been interpreted as a compensatory mechanism at the cortical level, where a larger extent of cortex affected by AD has to be activated in order to achieve similar performance as healthy people achieved with an activation of smaller cortical areas.

2.4.2. Activation studies with fMRI

In the 1990s functional magnetic resonance technique (fMRI) was developed, which has greater temporal and spatial resolution than PET, as well as not subjecting patients to ionizing radiation. However, studies of activation with biochemical markers are still more versatile and easier to carry out with PET.

The greater spatial resolution of fMRI compared to PET has allowed for a greater precision in the study of cortical activation patterns and thus more nuanced findings. As in PET studies, increased activation seems to reflect functional compensation for neuronal loss. For instance, with a semantic task there was significant correlation between activation and atrophy in the inferior frontal gyrus [54]. Likewise, a visuospatial task activated larger visual areas in the AD patients [55] and there was increased activation of a lateral temporal area for a semantic memory task [53]. The situation, however, is more complex. Hippocampus tends to be hypoactive, as well as some of the brain regions mediating category-specific semantic processing, such as the posterolateral temporal-inferior parietal cortex [53,55,56]. Thus, it is possible that activation could be bimodal, increasing with a slight or moderate neuronal dysfunction or loss, and decreasing when, with greater disease progression, the cortical neuronal networks become more severely impaired, as in the entorhinal cortex of the patients studied by Small et al. [56]. This hypothesis could be tested by studying the parieto-temporal activation of patients with more advanced disease. However, these patients are more difficult to study with fMRI because they are less likely to perform adequately the tasks needed for activation paradigms.

2.5. Magnetic resonance spectroscopy

Magnetic resonance spectroscopy (MRS) allows for the relative measurement of a number of chemical compounds important for brain function. N-acetyl aspartate (NAA) is decreased and myoinositol increased in a wide distribution of the hemispheres of AD patients [57]. MRS allows for the evaluation of phospholipid metabolites, which are abundant in synaptic membranes altered in AD. The concentration of phosphodiester and of glycerophosphoethanolamine has been associated with the amount of amyloid plaques and with the presence of psychotic symptoms, respectively [58,59]. Quantitative studies of all the compounds measurable by MRS in AD have shown that this technique has high sensitivity but low specificity [57]. However, comparing AD patients with controls, the addition of the local concentration of NAA to MRI volume measurements of medial temporal structures increased the classification accuracy significantly from 89% to 95% [60]. Studies comparing the yield of MRS in AD at 1.5 T and 3 T have not found a greater accuracy when working with the higher field strength [61].

2.6. Regional density of AD-relevant substances measured with PET

2.6.1. Amyloid plaques and neurofibrillary tangles

Several compounds are now available to detect amyloid deposition and neurofibrillary tangles in the AD brain by means of PET. FDDNP binds in vitro amyloid fibrils and neurofibrillary tangles [62]. In a pilot study with clinical PET in 9 patients with AD and 7 controls, this compound was eliminated more slowly from the brain of patients with AD [62]. Its possible clinical use is yet to be clarified.

More advanced is the testing of an uncharged derivative of thioflavine-T that has high affinity for Abeta fibrils and shows very good brain entry and clearance. Termed “Pittsburgh Compound B” (PIB) it has been tested in 16 patients with early AD [63]. Amyloid deposition was detected in all but 3 of the AD patients and in none of the controls. Amyloid was preferentially distributed in parieto-temporal and frontal association cortex and posterior cingulate cortex, regions known to have heavy amyloid deposition in AD [27]. [11C]PIB was used in this study [63]. Efforts are under way to commercialize an [18F] compound, with a longer half-life and easier use in a clinical setting.

2.6.2. Microglial activation

The brain of patients with AD contains activated microglia, which could mediate neuronal damage or simply contribute to cleaning neuronal debris, the result of the damage caused by other etiological agents. When cerebral microglia are activated, the expression of peripheral benzodiazepine receptors increases. Cagnin et al. [64] measured the regional cerebral density of the activated microglia with PET and carbon 11, marked with (R)-PK11195, which has a great affinity for peripheral benzodiazepine receptors. In 15 normal people, the density did not change with age, except in the thalamus, where there was an increase with age. However, 8 patients with AD and one person with MCI had an increased density in the entorhinal, temporoparietal and cingulate cortex.

2.6.3. Enzyme activity and receptor concentration

Several studies have shown that there is a loss of cortical acetylcholine esterase in AD [65–67]. This loss is in proportion to the cognitive impairment and the duration of the disease. However, it is more important in patients with early-onset AD, who also tend to have a greater neuronal loss. Interestingly, in early AD, binding to acetylcholine esterase receptors was decreased in cortex and amygdala,
but not in the region of the nucleus basalis of Meynert [68].

Acetylcholine esterase inhibition with drugs such as donepezil has also been studied with PET [69,70]. Thus, it has been determined that inhibition in patients treated with the usual doses (5 and 10 mg) is only partial, and reaches approximately 27% of the enzyme activity with both doses, without a dose–response curve. There is a great interest in obtaining a marker for choline-acetyl-transferase, an enzyme that is directly related to the degree of cognitive impairment, without the floor effect observed with acetylcholine esterase (37% in advanced AD) [66,67].

PET compounds that bind to neuronal receptors could be useful to detect regional neuronal loss in AD. However, neither the concentration of muscarinic cholinergic receptors nor the concentration of GABA A receptors has reliably separated controls from patients with AD [71–73].

3. Prediction of increased risk of AD at the MCI or presymptomatic stage

3.1. Structural MRI

3.1.1. Cross-sectional studies

Cortical measurements of the entorhinal cortex and banks of the superior temporal sulcus and anterior portion of the cingulate sulcus discriminated well normal elderly from those with MCI who went on to develop AD (accuracy of discrimination was 93%) [10]. However, there was only a 75% accuracy in discriminating between people with MCI who in 3 years of follow-up developed AD and those who remained stable [10]. Entorhinal measurements separated better than hippocampal measurements the normal individuals from those who were to develop dementia [74].

3.1.2. Longitudinal studies

The longitudinal progression of atrophy is predictive of cognitive decline in older people [75]. In a 6-year follow-up study of normal individuals older than 60 years, the atrophy rate of medial temporal structures separated those who developed cognitive impairment with a 91% specificity and 85% sensitivity [17]. In a study of subjects with familial AD, longitudinal, but not cross-sectional measurements distinguished them from controls [76]. At least annual MRIs were performed. In the familial cases, the rate of atrophy increased about 3 years before the individuals became symptomatic [76].

3.2. Prognostic value of metabolic studies with PET

Reduced metabolism in a network of limbic structures (hippocampal complex, medial thalamic region, mammillary bodies and posterior cingulate cortex) is characteristic of amnesic MCI [26]. AD patients have, in addition, reduced metabolism in amygdala and parieto-temporal cortex [26].

3.2.1. Prognostic value of parieto-temporal or posterior cingulate hypometabolism

Reiman et al. [77] were the first to report on the prognostic value of cortical metabolism studied with PET in healthy elderly people with an increased risk of having AD. In 37 patients with probable AD, cortical metabolism was reduced in the parieto-temporal association region and the posterior cingulate gyrus. These same areas were hypometabolic in a group of 11 elderly people without dementia but homocytogotes for the ApoE4 allele. Both groups were compared with a group of 22 elderly people of the same age with normal cognition. In the same patient sample, hippocampal volumes measured on MRI were about 8% smaller in the ApoE4 homozygotes than in the controls, not reaching statistical significance [78]. In a stepwise logistic regression model, posterior cingulate FDG PET measurements continued to distinguish ApoE4 homozygotes from non-carriers after adjusting for hippocampal volumes. However, the hippocampal volumes did not separate these two groups in a model already including posterior cingulate glucose metabolism. The authors concluded that PET appears to be more sensitive than MRI in identifying cognitively normal persons at risk for AD [78]. It must be noted that this was a cross-sectional study and that longitudinal MRI measurements were not available. The same researchers recorded decreased posterior cingulate metabolism in ApoE4 carriers in the 20–39 age range [79].

Other studies have confirmed the value of brain metabolism studied with PET in order to predict cognitive decline in those with MCI or with an increased genetic susceptibility. Small et al. [80] obtained FDG PET in 27 people with one or two ApoE4 alleles and in 27 controls without ApoE4 alleles. It must be noted that the ApoE4 group probably had MCI on initial evaluation (MMSE 28.0, Buschke 87.9), while the controls did not have memory problems (MMSE 29, Buschke 95.2). On the initial PET, the individuals with ApoE4 had reduced metabolism in the inferior parietal lobule, the lateral aspect of both temporal lobes and the posterior cingular cortex. Ten people in each group had a follow-up PET examination 2 years after the initial PET. Four of the ten elderly people with ApoE4, but none of those without ApoE4, had experienced a significant memory loss in the interval between the two studies. There was a correlation (Pearson, \(r = 0.69, p = 0.026\)) between memory loss and baseline parietal metabolism in the group of people with ApoE4, but not in the group without this allele [80]. Although closer inspection of their data seems to show that among those with MCI there were two subgroups, the small number of patients precludes the evaluation of the prognostic value of parietal hypometabolism.

In a study of 20 people with MCI, 10 developed AD in 3 years [81]. Of those 10 with a normal PET at the beginning of the study, 3 (30%) developed AD, while 7 (70%) of those with an abnormal PET developed AD. Although the
numbers are small, this study suggests that biparietal metabolism studied with PET could have a prognostic value in MCI. A similar result has been described more recently [82]. With a larger number and using a voxel-based comparison technique, an abnormal PET predicted the conversion to AD in a large MCI cohort [83]. Other studies, however, have postulated that a decrease in parieto-temporal metabolism occurs in AD, whereas MCI would be characterized by decreased medial temporal metabolism [25,26]. These studies seem to imply that patients with clinical MCI but with parieto-temporal abnormalities actually have AD.

Longitudinal studies of the yearly decline in glucose metabolism could be used advantageously to monitor the rate of decline in therapeutic trials. Using maximal glucose metabolism reductions in the left frontal cortex, Alexander et al. [3] estimated that as few as 36 patients per group would be needed to detect a 33% treatment response with one-tailed significance of \( p \leq 0.005 \) and 80% power in a 1-year, double-blind, placebo-controlled treatment trial.

3.2.2. Prognostic value of entorhinal hypometabolism

The entorhinal region, in the medial aspect of the temporal lobe, is the first to show amyloid plaques and neurofibrillary tangles in AD [84–86]. Furthermore, neuronal loss in this region already occurs in those with MCI [87]. However, this region has been difficult to study in detail "in vivo" until recently because of its small size, making it difficult to resolve with current clinical PET equipment. Coupling techniques of MRI and PET, de Leon et al. [25] measured metabolism in the entorhinal region in healthy elderly people and determined the difference between those who remained healthy and those who evolved to MCI or AD. In a 3-year longitudinal follow-up, 12 out of 48 normal elderly people developed cognitive impairment, MCI (11) or AD (1) [25]. In the baseline study, at the beginning of the 3 years, glucose metabolism was reduced in the entorhinal cortex by 18% in those who later developed cognitive decline. In those elderly people who were carriers of the E4 allele, metabolism was also reduced in the lateral temporal cortex (8%) and in the superior temporal gyrus (3%). However, when an individual who developed AD was set aside, only decreased entorhinal cortex metabolism (17%, \( p < 0.001 \)) separated the ones who remained healthy from those with MCI. This study suggests that more detailed functional neuroimaging of this region, with equipment with a greater spatial resolution than the 5–7 mm of a conventional PET, could allow for a more accurate prediction. This type of equipment, with a resolution of 1.5 mm in three dimensions, is already available (micro PET) for the study of experimental animals [88]. On the other hand, it is possible that the earliest metabolic changes corresponding to the entorhinal neuropathology occur not in the medial temporal region, but in cortex to which it projects, namely the lateral parieto-temporal regions and the posterior cingulate region. These areas have decreased metabolism even in asymptomatic ApoE4 carriers in the third and fourth decades of life [79].

3.3. Regional cerebral perfusion: areas of hypoperfusion on SPECT that predict decline to probable AD

Using a statistical factorial system, Johnson et al. examined the difference between controls and those who had developed Alzheimer’s, comparing the SPECT studies carried out when both groups were asymptomatic [36]. Presymptomatically, those who developed Alzheimer’s disease showed a decreased perfusion in the hippocampus, anterior and posterior cingulate gyrus, and dorsomedial and anterior nucleus of the thalamus, all of them structures with an important role in memory and attention. This finding had a sensitivity of 78% and a specificity of 71% [36].

The same group studied with perfusion SPECT a family with a presenilin 1 gene [89]. Of this family, 23 people did not have the gene, 18 had it but were cognitively intact and 16 had already shown signs of cognitive impairment. Compared with those who did not have the gene, those who did have it, but without cognitive impairment, had decreased perfusion in the hippocampus, anterior and posterior cingulum, and parietal and frontal association cortex. This pattern on perfusion SPECT could separate correctly 86% of gene carriers and controls, indicating that there are abnormalities in cerebral perfusion even in asymptomatic individuals with a presenilin 1 gene.

3.4. Activation studies with functional magnetic resonance imaging

Small and collaborators studied the entorhinal, subiculum and hippocampal cortex in 4 elderly people without cognitive impairment, 4 with AD and 12 with MCI. In this last group they found 8 with normal entorhinal cortex activation and the other 4 with a pattern of lack of activation similar to the one discovered in the 4 patients with AD [56]. On follow-up, these patients tended to worsen to AD (GW Small, personal communication). In another study, the activation paradigm consisted of remembering a geometric drawing [55]. Subjects with early AD (\( n = 7 \)) did not activate entorhinal cortex, supramarginal gyrus or prefrontal region, all on the right side, in contrast to the normal controls [55].

Considered superficially, these data seem to clash with results obtained from a larger fMRI activation study in which people with the ApoE4 allele had a higher degree and extent of cortical activation than homocytotes for the ApoE3 allele [90,91]. Bookheimer and collaborators studied 30 cognitively normal subjects with fMRI [91]. Of these subjects, 16 had the ApoE4 allele and the remaining 14 were homocytotes for ApoE3. The activation paradigm consisted of trying to remember pairs of words not related to each other, and therefore explored episodic verbal memory. As expected from the activation paradigm, the left perisylvian cortex and hippocampus were activated in both groups.
However, those with the ApoE4 allele had a larger activation of the hippocampal gyrus, dorsal prefrontal cortex, parietal lobe and anterior portion of the cingulate gyrus. Two years after the baseline study, the neuro-psychological memory studies were repeated in 14 subjects, proving that there was a positive link between the number of regions activated in the functional MR study and the degree of verbal memory reduction measured with the Consistent Long-Term Retrieval section of the Buschke-Fuld Selective Reminding test [91]. A similar result for the medial temporal section of the Buschke-Fuld of verbal memory reduction measured with the regions activated in the functional MR study and the degree proving that there was a positive link between the number of psychological memory studies were repeated in 14 subjects, cortex, parietal lobe and anterior portion of the cingulate of whom declined over a 2.5-year follow-up [92]. The decliners activated a greater portion of the right parahippocampal gyrus in the baseline study, despite equivalent memory performance [92]. It is possible that those with neuronal loss or dysfunction need more extensive cortical activation in order to carry out the same cognitive task. In another situation in which demand on the cortex is greater, such as in the learning process, larger areas of the cortex are activated than when the learning process is complete and the task can be done more quickly and easily [93]. It is also possible that activation could be bimodal, increasing with a slight or moderate neuronal dysfunction or loss, and decreasing when, with greater disease progression, the cortical neuronal networks become more severely impaired, as in the entorhinal cortex of the patients studied by Small et al. [56].

The finding of greater activation in more impaired patients could be selective for episodic memory and for semantic tests [54], because it has not happened with other cognitive tests [94].

In conclusion, longitudinal measurements on structural MRI or PET FDG studies seem currently most robust to evaluate progressive impairment in MCI and AD by means of neuroimaging. Applied to subjects at risk, such as with an abnormal presenilin gene or an ApoE4 allele, measurements of progression of entorhinal cortex atrophy or posterior cingulate metabolism could predict the onset of memory loss several years before it actually happens. This is exciting, because the effect on atrophy or metabolism of potential therapies could be evaluated in the presymptomatic stage.

A number of new PET ligands now permit the detection “in vivo” of some of the changes associated with AD, such as microglial activation and amyloid deposition. It remains to be determined whether these changes can be detected in MCI or in the presymptomatic stages and perhaps serve as surrogate markers for therapeutic trials.

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