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Currently Available Neuroimaging Approaches in Alzheimer Disease (AD) Early Diagnosis

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1. Introduction

Alzheimer´s disease (AD) is a condition mainly diagnosed through clinical interpretation and neuropsychological testing. Unfortunately this leads to problems due to variations in expertise of the clinicians involved. Moreover, its diagnosis is usually achieved in later phases of the disease, which reduces the scope of useful interventions. In this chapter we will review the different brain imaging approaches used for both AD and mild cognitive impairment (MCI), a condition which evolves into AD in an important proportion of cases (between 10-15 % yearly) (Petersen, 2008).

It has been hypothesized that the accumulation of β-amyloid (Aβ) in the AD brain triggers a cascade of neurodegenerative events, including inflammatory processes, neurofibrillary tangles, oxidative stress, and neuronal network dysfunction with synaptic loss and neurotransmitter deficits. Such events are manifested by progressive impairment of cognitive functions (Kadir et al, 2011). Years ago, an accurate diagnosis of AD was considered only possible using a demonstration of Aβ plaques and neurofibrillary tangles at post-mortem histopathological analysis of the brain (Wiley et al, 2009).

At present there are promising methods for the *in vivo* assessment of the extent of AD. The typical findings of these brain imaging techniques are different and they are summarized in Table 1. These neuroimaging methods may help in AD early diagnosis as well as helping in differentiating AD from other neurodegenerative conditions. Although some pioneering work started in the 1970s, the explosion of knowledge regarding brain imaging methods for AD diagnosis is a matter of the last two decades.

1.1 Computerized Tomography (CT)

Nowadays CT is not considered a standard technique for diagnosing AD, least of all in early stages. Its main usefulness is in differential diagnosis since it is less expensive, faster and more widely available than MRI. CT allows ruling out some clinical situations which lead to

behavioural alterations but are not AD, e.g., normotensive hydrocephalus, intra and extra-axial bleeding, etc.

Neuroimaging technique	Finding
CT	Tissue atrophy.
MRI	Tissue atrophy. It is more specific about grey matter.
fMRI	Changes in blood oxygenation level (BOLD signal) representing synaptic activity.
DTI	Connectivity and organization in white matter tracts.
Spectroscopy	Chemical content of the brain, such as NAA/Cr ratio or others.
SPECT	Changes in cerebral perfusion.
PET	Changes in glucose metabolism.
PET-amyloid	Measures accumulation of β-amyloid, an AD-specific protein.
MEG	Measures magnetic fields and, indirectly, yields rather precise information about brain electrical activity

CT = computerized tomography; MRI = magnetic resonance imaging; fMRI = functional magnetic resonance imaging; DTI = diffusion tensor imaging; SPECT = single-photon emission computed tomography; PET = positron emission tomography; MEG = magnetoencephalography; BOLD = blood oxygen level-dependent; NAA = N-acetyl aspartate; Cr = Creatinine; AD = Alzheimer's disease

Table 1. Typical findings of different brain imaging methods used in AD and MCI diagnosis

1.2 Magnetic Resonance Imaging (MRI)

1.2.1 Structural MRI

This technique provides the best possible spatial resolution. Given the fact the most robust neuroimaging finding in AD is the atrophy of mesial temporal structures, structural MRI is the most widely used approach. Hippocampal atrophy is another well known finding, but atrophy within other brain areas has also been described in entorrhinal cortex, amygdala, basal ganglia (nucleus basalis of Meynert), thalamus and bilateral parietal cortex. It is relevant to mention here that in terms of early diagnosis some consider the entorrhinal cortex as the earliest area affected by AD. Other researchers have stated that the nucleus basalis of Meynert is a key structure in AD early diagnosis (Herholz et al, 2004; Grothe et al, 2010).

1.2.2 Functional MRI (fMRI)

fMRI provides signal intensities images associated with a relative cerebral blood flow during cognitive tasks. Resting and activation functional MRI studies have showed a lesser coordinated activity in the hippocampus, inferior parietal lobes –both bilaterally- and cingulate cortex in patients with AD. This neuroimaging technique is nowadays used to monitor AD patients' treatment.

Combining genetic risk with functional MRI memory task paradigms has shown to be a very accurate pre-symptomatic predictor of cognitive decline.

1.3 Diffusion Tensor Imaging (DTI)

DTI allows visualizing neuronal connectivity or, more precisely, local fiber orientation and white matter tracts integrity. Patients with AD show decreased fiber density in temporal white matter, probably related to the medial temporal grey matter atrophy, as well as in the splenium of the corpus callosum.

In mild cognitive impairment (MCI), however, this decreased fiber density has been located in the anterior part of the corpus callosum.

1.4 Spectroscopy

It provides information on tissue substrate or metabolite concentrations. Specifically the N-acetyl aspartate (NAA) has been used as a biomarker of neuronal death, and it has been demonstrated that in patients with MCI and AD is significantly reduced compared to healthy controls.

1.5 Nuclear medicine brain imaging techniques

1.5.1 Single-photon emission computed tomography (SPECT)

It measures cerebral flow by detecting a single-photon emitting tracer after its intravenous injection and brain uptake. It has a very low spatial resolution and its diagnostic accuracy is lower than PET. Nevertheless, in clinical practice, it can be useful for differentiating AD from other dementias such as frontotemporal dementia.

1.5.2 Positron emission tomography (PET)

Recently a new technique using PET with Pittsburg compound B (PIB; PIB-PET) has emerged. PIB is a tracer which allows marking β-amyloid plaques. This technique has been highly efficacious to detect β-amyloid *in vivo* and, therefore, could be rather useful to detect AD in its early phases.

1.6 Magnetoencephalography (MEG)

MEG is a technique which measures brain magnetic fields both during basal state and during cognitive activation. Its time resolution is measured in milliseconds. It is precisely this very high temporal resolution which allows evaluating small changes in brain processing during cognitive stimulation. These changes may help to differentiate between AD, MCI and normality as well as providing some clues about differences in information processing in these same conditions

Different studies carried out with MEG show a decrease in magnetic fields in people with AD in temporal mesial areas during memory tasks. People suffering from AD exhibit increased slow frequencies in temporoparietal areas in basal evaluation.

2. Computed Tomography (CT)

Since the 1970s, there have been many CT studies searching for evidence of focal atrophy in the brains of subjects with AD (DeCarli et al, 1990). The search was complicated by the overlap between changes common to AD and normal ageing and because AD cases were only diagnosed clinically (Smith and Jobst, 1996). There are both generalized and focal changes, both in cortical areas as in the ventricular system, in brain atrophy. Unfortunately focal atrophy is not consistently found in standard axial CT studies though subjects with AD may show a greater degree of generalized atrophy revealed by sulci enlargement and ventricular dilatation.

DeCarli et al (1990) concluded as follows: “Unfortunately, at present there is little definite evidence for clear anatomic brain changes that accurately predict the cognitive dysfunction within a group of patients suffering Alzheimer’s disease”. The dictum still remains valid.

The standard axial CT system used internationally does not show the medial temporal lobe well, mainly because of the scan angle used. Changes in the medial temporal lobe itself have to be inferred from dilatation of the temporal horns of the lateral ventricles and enlargement of the suprasellar cisterns. Indeed, these changes have been observed in AD (Kido et al, 1989). By 1988, an alternative camera angle was used for hippocampus evaluation in patients with temporal lobe epilepsy and this system was also used by de Leon et al (1989) to study AD patients. The angle is parallel to the long axis of the temporal lobe and scanning is carried out from below and upwards until the inferior margin of the orbit is reached; in this way a complete series of images through the temporal lobe is obtained without exposing the eyes. Using this "temporal-lobe-oriented" CT procedure, de Leon et al (1989) found that 87% of patients with moderate to severe AD had dilatation of the hippocampal fissure compared with age-matched controls.

Hippocampal atrophy detected with CT was also more common in a group that did not reach the clinical research criteria for AD but showed minimal memory impairments. This led them to suggest that hippocampal atrophy might be an AD marker which occurs early in the course of the illness, before the diagnosis is established, and predicts deterioration (De Leon et al, 1989). Hippocampal atrophy is not the only neuroimaging sign in AD, but it is rather characteristic.

The axial temporal lobe oriented CT scan can be used to look for other possible causes of dementia, such as multiple infarcts, tumours or hydrocephalus, and the temporal lobe-oriented scan (in 1.5-2 mm slices) to reveal atrophy of the medial temporal lobe (Smith et al, 1996) (Fig 1).

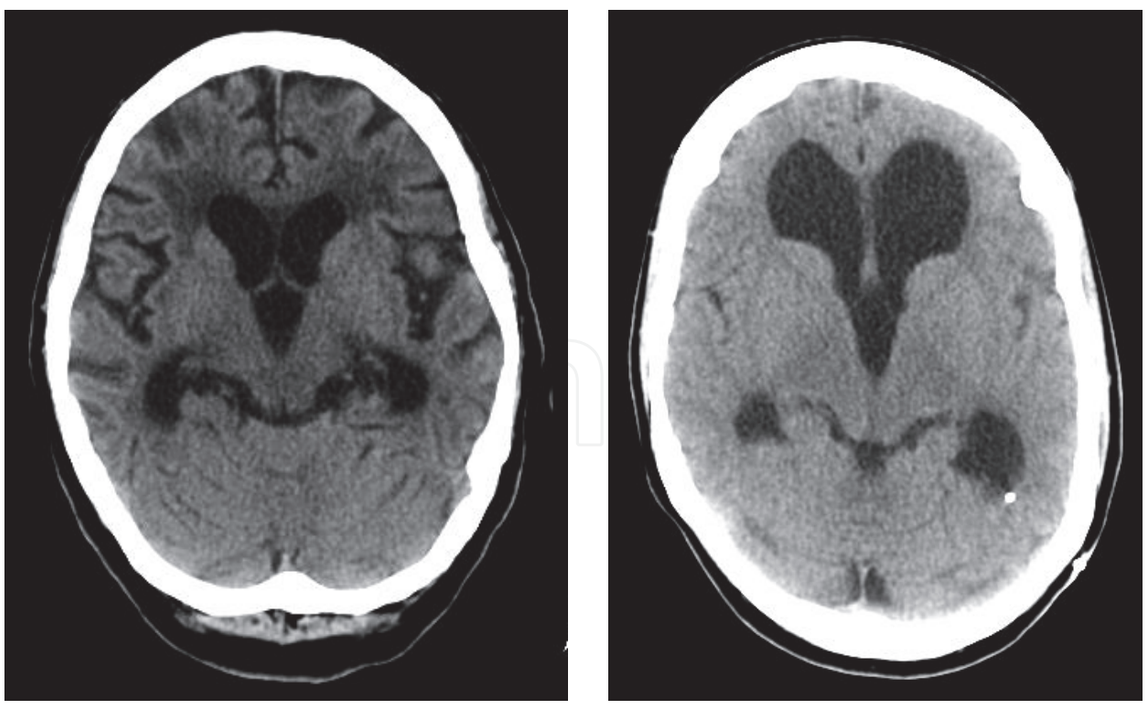

Fig. 1. CT in AD on the left and a patient with normotensive hydrocephalus on the right, where a catheter can be seen. CT is helpful to differentiate between AD and other brain conditions.

Unfortunately CT usefulness in AD diagnosis is very limited (DeCarli et al, 1990). In the last 20 years MRI became increasingly available and the vast majority of structural neuroimaging used since then has been MRI. This is the reason why there are no relevant papers written since then where CT has been used for AD.
Atrophy is evident, at hippocampal level too. Dilatation of the lateral ventricles can also be seen.

3. Structural magnetic resonance imaging (MRI)

MRI volumetry was one of the earliest brain imaging techniques used to identify AD. Given the temporal lobe atrophy found in AD patients, it seemed that this finding per se could diagnose AD. Further research revealed this simplistic approach was flawed.
The first technique was manual volumetry. This required an excellent working knowledge of neuroanatomy as well as good dexterity in delineating the ROIs (regions of interest). This method is highly operator-dependent and multiple subjective issues can arise. This is overcome by double or triple-blind studies. Manual volumetry is also very time-consuming. On the other hand you have to have a prior hypothesis, such as a ROI to analyze. There have been many hypotheses in AD. Hippocampal analysis stands out (Besga et al, 2010) amongst them, though more recently other structures, such as the caudate nucleus or thalamus (Skup et al, 2011), or even corpus callosum, are being considered.
A newer method is the so-called Voxed-based morphometry (VBM). This is an authomatized approach which allows distinguishing between grey and white matter. It also allows performing statistical studies amongst different populations (Kinkingnéhun et al, 2008).
Multiple computer techniques have evolved since then. They allow analysing the brain, either globally or in any 3D ROI. For instance, in hippocampus, a key structure in AD, there are "radial atrophy mapping approach" or "large-deformation high dimensional brain mapping". The former computes the 3D distance from the hippocampal centroid in each coronal section (also called a medial curve or core) to each hippocampal surface point. This provides an intuitive 3D measure of hippocampal thickness, as well as metric estimates of hippocampal atrophy that can be compared point-by-point across individuals and groups (Thompson et al, 2004). The latter is also used to study the changes in hippocampal morphology in patients with AD (Apostolova et al, 2007). Rather than relying on hippocampal manual tracings, a template hippocampus is traced on a single subject and fluidly warped to match the anatomy of new subjects. The transformation involved is high-dimensional, i.e. involves millions of degrees of freedom to produce a deformation that captures shape differences in detail. It is *de facto* a 'large-deformation' approach, that is to say the deformation model follows a continuum-mechanical law that prevents folding or tearing of the deforming template (this is known mathematically as a *diffeomorphism*).
Similarly to VBM, many cortical computational anatomy techniques use the segmented grey matter maps and the grey matter density approach (Thompson et al, 2004) or a more advanced grey matter thickness approach (Lerch et al, 2005; Singh et al, 2006; Apostolova et al, 2008).
Using the hippocampal radial atrophy mapping approach, Thompson et al (2004) showed profound hippocampal differences between normal controls and AD patients. These differences were correlated with MMSE scores. Two cross-sectional large-deformation high-dimensional brain mapping hippocampal studies have suggested the CA1 subfield may

discriminate between normal aging and questionable AD (Clinical Dementia Rating Scale (CDR) = 0.5) (Csernansky et al, 2000; Wang et al, 2006).

Along the last 10 years all sorts of volumetry studies aiming at early diagnosis of AD have been carried out. They mainly focus on either comparing AD versus MCI or healthy controls category or finding AD progression biomarkers progression.

One can reliably classify AD patients and controls in the first group. Most studies revolve around temporal mesial lobe (MTL) structures. Many volumetric MCI studies measure hand-traced ROIs of specific MTL structures and most of them focus on the hippocampus. The majority of published studies indicate MCI patients have less hippocampal volume than cognitively intact controls (Becker et al, 2006; Kantarci et al, 2002), and AD patients have less volume than those with MCI (Wolf et al, 2004).

Other studies show average entorhinal cortex volume in MCI patients is decreased compared with cognitively intact controls. Cross-sectional ROI studies have shown that the hippocampal and entorhinal volumes (Juottonen et al, 1999; Xu et al, 2000) can reliably differentiate AD subjects from normal older adults. Although some researchers claim that the precision of differentiating MCI from normal controls and MCI from AD is substantially less accurate when using hippocampal volume (MCI vs controls: sensitivity = 52– 80 % and specificity = 79–80% ; MCI vs AD: sensitivity = 45–60 % and specificity = 80%) than when using entorhinal cortex volumetry (Xu et al, 2000; Du et al, 2001; Kantarci et al, 2002), they concluded that, given the ambiguity imposed by the boundaries of the entorhinal cortex, it is easier to make these measurements in the hippocampus. Which structure is the more powerful discriminator to distinguish MCI patients from normal controls is currently being debated. Some studies side with the hippocampus and others with the entorhinal cortex (Pennanen et al, 2004).

The second group of studies is made up of longitudinal research based on disease progression. Two hypotheses have emerged: the degree of atrophy progression and the basal atrophy found in AD patients.

Several longitudinal studies have examined the relationship between the brain atrophy rate and its progression from MCI to AD. They have found significant group differences between MCI patients who progress to AD versus those who do not rapidly progress. They show that the hippocampus shows higher annual rates of atrophy in patients with MCI that progress to AD than in those who remain stable (Chetelat et al, 2005; Apostolova et al, 2006; Jack et al, 2004). Others have found that entorhinal cortex atrophy rate, but not hippocampus, is faster for individuals progressing to AD (Stoub et al, 2005). Moreover, other studies have shown that not only mesial temporal lobe regions show greater atrophy linked with progression towards AD, but also some cortical structures, such as posterior cingulum, precunneus or temporal medial lobe (Jack et al, 2004; Jack et al, 2005; Chetelat et al, 2005).

Several studies have examined the accuracy of a single baseline brain MRI in predicting the progression towards AD, or stability, using a longitudinal clinical status follow-up. Studies using VBM for whole-brain analysis also find that a lower hippocampal baseline predicts progression towards MCI (Whitwell et al, 2007; Chetelat et al, 2005; Bozzali et al, 2006). Others studies using manual tracing methods have failed to replicate this association and report the entorhinal cortex as a more sensitive predictor of progression (de Toledo-Morrell et al, 2004; Stoub et al, 2005).

Investigations using VBM have identified areas outside the mesial temporal lobe in which lower baseline volume in certain areas is related to later progression to MCI. These areas are

fusiform gyrus (Whitwell et al, 2007; Chetelat et al, 2005), medial and inferior frontal regions (Whitwell et al, 2007; Bozzali et al, 2006) and the posterior cingulate and precuneus ones (Whitwell et al, 2007; Hamalainen et al, 2007).

To summarize, it is in the last decade when we have been able to have an accurate idea about the structural brain changes in MCI as well and its progression towards AD. Those structural changes are multiple. Hippocampal atrophy is important, but there are also other important cortical biomarkers. Atrophy is more diffuse than one would expect, but pinpointing the specific regional areas of atrophy can be useful in the diagnosis of AD and differential diagnosis with other types of dementia. VBM is a technique which can help in identifying the regions of atrophy.

Nevertheless it is important to take into account that all these studies are population ones, so none of them serves as an individual maker. Though reliable whole brain measurements can be accomplished with authomatized methods there is no way yet to know which MCI patients will evolve into AD. However these structural ancillary tests are clinically useful in combination with neuropsychological testing, augmenting significantly the prognosis accuracy.

4. Functional magnetic resonance imaging (fMRI)

It can be described as a non-invasive form (it does not require the injection of a paramagnetic contrast) of MRI. It measures the oxygen consumed by certain brain areas when they are challenged with specific stimuli or tasks. This technique has got a high spatial resolution and a rather acceptable temporal resolution too. Its major inconvenience is its high sensitivity to small head movements. It is carried out taking brain images during a specific activity and in basal state. Basal state activity is subtracted from the specific task activity to yield the specific brain areas where blood flow has increased due to the specific activity tested.

fMRI physical foundation relies on the inherent magnetic properties of blood. Red blood cells (RBC) have a haemoglobin molecule which has an iron (Fe) atom in its centre. Oxygen binds to haemoglobin yielding oxihaemoglobin and haemoglobin configuration changes when oxygen is delivered to tissues (deoxihaemoglobin). Both oxihaemoglobin and deoxihaemoglobin have different paramagnetic properties. Deoxihaemoglobin will create an in-homogeneous magnetic field around itself which will lead to a decreased signal. In other words, when there is less deoxihaemoglobin (and more oxihaemoglobin) due to increased activity and subsequent increased blood flow and associated oxygen concentration within a specific area, there will be a greater signal. Blood oxygenation dependent level (BOLD) gives a variable signal intensity between stimulus and resting state. BOLD signal relies upon the different magnetic susceptibility of oxyhaemoglobin and deoxyhaemoglobin (Westbrook, 2000).

Task testing is prepared according to paradigms. There is a huge variety of paradigms depending on the task. Broadly speaking these paradigms are classified into two main groups: “block design” or “event-related”. The former are characterized for stimulus presentation for a longer time while in the latter group they are presented for a shorter time and in an alternating fashion.

Numerous studies have shown activation during memory tasks in the anterior hippocampal region in both healthy older adults and young people. This activation has a lesser extension in healthy older adults. On the other hand healthy young adults exhibit a greater activation of the prefrontal cortex and a lesser parietal cortex activation in comparison with older adults (Sperling, 2003b).

AD patients show a consistent decreased activation in hippocampal and parahippocampal areas in comparison with healthy controls (Pariente, 2005). Dickerson et al (2004) suggested the cognitive deterioration degree could be inferred from the hippocampal activation at the time of fMRI basal scanning; the more hippocampal activation, the greater the deterioration. Interestingly, an increased activity in some neocortical regions has also been described (Sperling, 2003). This may be understood as a hippocampal failure compensatory mechanism. In fact these frontal regions have been labelled "default mode network", implying that AD patients would have difficulty in deactivating them (Buckner, 2005).

There are few fMRI studies addressing the differences between MCI and healthy adults. Moreover, their results show disparity, from mesial temporal lobe hyperactivation (Dickerson, 2004) to hypoactivation (Johnson, 2005).

Dickerson et al (2004) have tried to clarify this issue and they state that whenever there is MCI, there is a compensatory hyperactivation, and both the extension and localization of this compensatory activity depends on memory tasks demands and memory performance. They also affirm that memory starts to fail in advanced MCI stages, which is shown by hippocampal hypoactivity. In this way they describe an fMRI activity non-linear trajectory in a patient which evolves from MCI to AD, presenting first a hyperactivity phase in pre-clinical stages followed by an activation decrease. This is what they called "inverse-U shape curve" (Sperling, 2007; Dickerson, 2008). This curve poses a problem if it is used as an AD biomarker, namely the brain activity pseudo-normalization when people with MCI start deteriorating more and at that moment they show a loss of the MCI characteristic hyperactivation. They conclude that if there is minimal clinical symptomatology and little atrophy of the mesial temporal lobe for a given degree of hyperactivation and more clinical symptomatology with greater mesial temporal atrophy for the same degree of activation, we are in the ascending and descending parts of the inverse-U shape curve.

Johnson et al (2004) used a paradigm with repetitive presentation of faces to prove MCI patients do not show the same slope of decreasing hippocampal activity than in healthy older controls. This suggests a certain disruption of this adaptive response in the medial temporal lobe.

Dickerson (2008) stated the direct linear relation between the clinical deterioration and the extension of activity (measured as a function of the number of activated voxels) detected by fMRI both in hippocampus as in parahippocampus. Thus, a greater clinical deterioration correlates with a greater activity extension in the mesial temporal lobe which, in turn, correlates negatively with the degree of hippocampal atrophy.

Amongst those studies where different patient groups have been compared (healthy ones, very mild MCI, MCI and AD), Celone et al (2006) stands out because of the strong correlation they found between the degree of preserved memory and the activity of mesial temporal areas and deactivation of precunneus and parietal cortex, using always a "default-mode network" approach.

5. Diffusion tensor imaging (DTI)

This technique is also known as diffusion MRI. Its underlying physical basis relies upon detection and quantification of the random movement of water known as the Brownian movement. Molecules undergoing the Brownian movement follow a chaotic route due to continuous impacts against other particles in their environment and their speed is directly proportional to the system temperature.

Even though the system displacement induced by a single hydrogen molecule cannot be appreciated, the impacts of a great number of them generate a significant and quantifiable displacement of a chaotic nature. However it is possible to calculate the distance run by a particle in a given time through the formula: $R=\sqrt{6}\ D\ \tau$. D is the molecule diffusion coefficient, which is dependent on the temperature, while τ is the time interval. In biological tissues D is not the only cause of molecular movement since microcirculation, amongst other variables, throughout the capillary net has a diffusion increase net effect. This is the reason the term apparent diffusion coefficient (ADC) is used.

When the diffusion in a structured system, such as the brain, is quantified, molecules displacement is limited by physical barriers. The latter make the displacement dependent upon direction (anisotropy). In a system without barriers a particle undergoing the Brownian movement can displace freely in any direction, with an isotropic diffusion. Whenever there are physical barriers, such as a membrane or axonal fibres, the particle loses movement freedom and the diffusion is therefore restricted (anisotropic).

A set of DTI images permits the identification of a predominant direction of diffusion (anisotropy). The processing of diffusion values is carried out through a structure called tensor. A tensor can be defined as a set of co-existing magnitudes dependent upon direction and coordinates.

Tractography permits the reconstruction and 3D visualization of the neuronal column structures. If is applied to white matter axon fibres, it provides information about connectivity and fibre deviations caused by tumours and infarcts (Martí-Bonmatí, 2008; Le Bihan et al, 2001; Melhem et al, 2002).

In short, MRI water diffusion measurements include those images weighted in diffusion (DWI) and tensor diffusion (DTI). DWI provides a mean without direction (isotropic) of tissue water diffusivity. DWI is described in terms of ADC. ADC increases reflect neuronal loss and increased extracellular space, where water diffusion is faster, and it is an indirect indicator of grey or white matter integrity. DTI can be understood as an index of tissue permeability difference in different directions (anisotropic) and it is measured in terms of mean diffusivity (MD). Another important measurement to take into account is the anisotropic fraction (AF). AF is very sensitive in the evaluation of the microstructure integrity of the white matter. AF is obtained measuring water diffusivity along white matter long tracts (Ries et al, 2008).

The use of diffusion techniques is justified because of the AD ethiopathogenic mechanism, e.g., β-amyloid depositions and neurofibrillary tangles. They seem to interfere with neuronal function at early stages producing a cascade of ultra-structural changes in axons. The resulting damage affects axonal transport, microtubules structure, neurofilaments and the integrity of the myelin sheath (Englund, 1981). All of these factors produce microstructural changes in the white matter which, in turn, affect the water protons diffusivity, a parameter measurable by DTI. This technique has the advantage of being very sensitive in detecting microstructural abnormalities, something not revealed by volumetric measurements.

The loss of tissue organization causes a decrease in anisotrophy (or its correlate, AF). It is assumed that reduced water diffusion parallel to axonal tracts is indicative of axonal degeneration, disruption and partial breakdown of cytoarchitecture (Beaulieu, 2002) or demyelinating processes (Song et al, 2002), which modifies AF.

We should focus on the corpus callosum (CC), the largest white matter structure in the brain. The CC provides inter-hemispheric communication and anterior-posterior

connections which link cortical association areas. CC anisotropy decreases with age. Progressively reduced AF has been reported as part of the normal aging process (Sullivan et al, 2010). This AF decrease seems to follow an anterior-posterior gradient. The genu has a lower AF compared to the splenium. Several major white matter fibre bundles, including those connecting to the hippocampal structures, pass through the genu of the CC (Serra et al, 2010).

Anatomical localization of AF reductions in amnestic MCI (aMCI) seems to be a robust finding across a variety of approaches. Thomann et al (2006) found an AF reduction in the rostral subregions and anterior body of the CC in MCI patients compared with healthy controls using region of interest (ROI) methods. Similarly Wang et al (2009) and DiPaola et al (2010), using voxel based morphometry (VBM), identified a density reduction in the genu in aMCI patients compared with healthy controls. Other researchers like Ukmar et al (2008), Cho et al (2008) or Parente et al (2008) found an AF reduction in MCI patients in the CC splenium. The splenium of the corpus callosum, crux of the fornix (Zhuang et al, 2010) and the cingulum were sensitive discriminators to differentiante between aMCI and normal subjects (Chua et al, 2009). Ortiz Alonso et al (2000) found a volume reduction of the anterior body, mid body and isthmus of the corpus callosum in a homogenous group of moderately advanced AD compared with healthy controls.

Several theories have been proposed to explain the early involvement of frontal white matter in MCI. The pattern of white matter integrity disruption tends to follow an anterior-posterior gradient with greater damage noticeable in posterior regions in AD and MCI. The aMCI group showed significant macrostructural atrophy only in the anterior CC section. In the mild AD group this atrophy extended to posterior CC subsections and was accompanied by anterior and posterior microstructural modifications (Di Paola et al, 2010).

It has been recently suggested that myelin breakdown is an important component of the illness process in AD (Bartzokis, 2004; DiPaola et al, 2010). According to this hypothesis late myelinating fibers should be more susceptible to myelin breakdown. This may constitute an alternative mechanism which may explain AD cortical progression in the direction opposite to myelination (Braak and Braak, 1997). Wallerian degeneration affects the posterior CC sub-region that gets afferent axons directly from those brain areas primarily affected in AD (temporoparietal regions). However the myelin breakdown process might affect the late myelination of the CC subregion, causing changes in the CC genu at early stages of the disease (DiPaola et al, 2010).

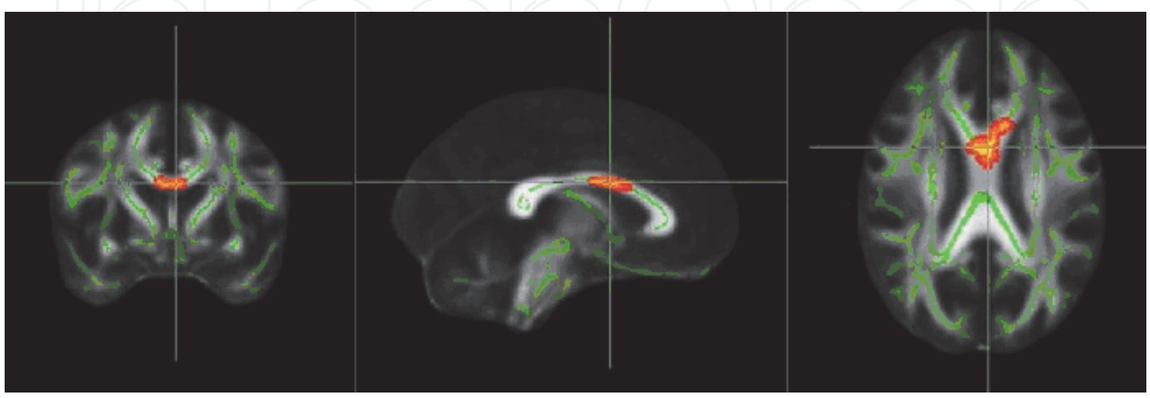

Fig. 2. Coronal, sagital and axial planes DTIs showing AF differences between patients with MCI and controls.

The controversial results concerning CC regional atrophy are most likely due to the methods adopted in various studies, such as different criteria used to select patients, different stages of the illness or variation in the number of participants. Those investigators who found that the genu was more adversely affected thought that earlier affectation of late maturing regions might be responsible, whereas others who found that the splenium was more affected said it might be due to the overall degenerative pattern occurring in the posterior circuitry of the temporal parietal areas.
A positive correlation between AF values and MMSE scores has been demonstrated in several studies, arguing in favour that white matter degeneration has an impact in cognitive performance (Bozzali, 2002; Ukmar et al, 2008; Ortiz-Terán et al, submitted) Other studies (e.g., Sullivan et al, 2010) found a correlation between AF decline in the CC with performance on the alternate finger tapping test, which is a test of inter-hemispheric communication transference.
DTI is more used nowadays for correct identification of dementia subtypes.

6. Magnetic Resonance Spectroscopy (MRS)

MRS is used to measure the levels of different metabolites in body tissues. It detects and quantifies resonance signals of certain molecules present at much lower concentrations (approximately 10^{-3} mol/g_{tissue}) than water ones (circa 55 mol/g_{tissue}). The metabolic profile of a concrete region within a specific organ can be obtained through a single voxel MRS (SVMRS) or through multivoxel MRS imaging. SVMRS provides a metabolic information average score within the selected voxel while multivoxel MRS provides, within a unique image acquisition, various molecular images which indicate the spatial distribution of different metabolites (Martí-Bonmatí, 2007).
The major drawback of SVMRS is the lack of spatial information, though the magnetic field homogenization is excellent and, consequently, so is its spectral resolution. On the contrary, multivoxel MRS yields spatial distribution information of different metabolites but its magnetic field homogenization is rather complicated since the brain areas are bigger and their magnetic susceptibility differences greater. Hence the characterization of a given specific volume is more precise with SVMRS but multivoxel MRS generates additional molecular information about surrounding areas. The latter provides more information about the heterogeneity of the lesion, analyzes peripheral infiltrations and allows comparisons with contralateral areas (Martí-Bonmatí, 2007).
The most common CNS metabolites measured with MRS are (1) N-acetyl-aspartate (NAA), a neuronal marker localized in neurons and axons, (2) choline (Cho), a marker which indicates membrane changes, (3) Creatine/phosphocreatine (Cr/PCr), an index of energetic metabolism, (4) lactate (Lac), a final product of glycolisis generated because of oxidative metabolism failure which is found both in intra and extra-cellular compartments, but never found in healthy tissues, (5) myoinositol (mI), mainly found within astrocytes where it regulates the cell volume, (6) lipids (Lip) and polypeptides, mostly in myelin sheaths and cell membranes and (7) glutamine (Gln) and glutamate (Glu), important neurotransmitters involved in multiple synaptic processes which give complex signals because of their ubiquity, scalar coupling and multiple complexes therefore posing a real challenge for their quantification.
In short, MRS is the only available technique for obtaining fast and simultaneous metabolic information *in vivo* and different molecular images within a single image acquisition. It is a

reliable method for clinical molecular follow-up and studying therapeutic effectiveness in different diseases.

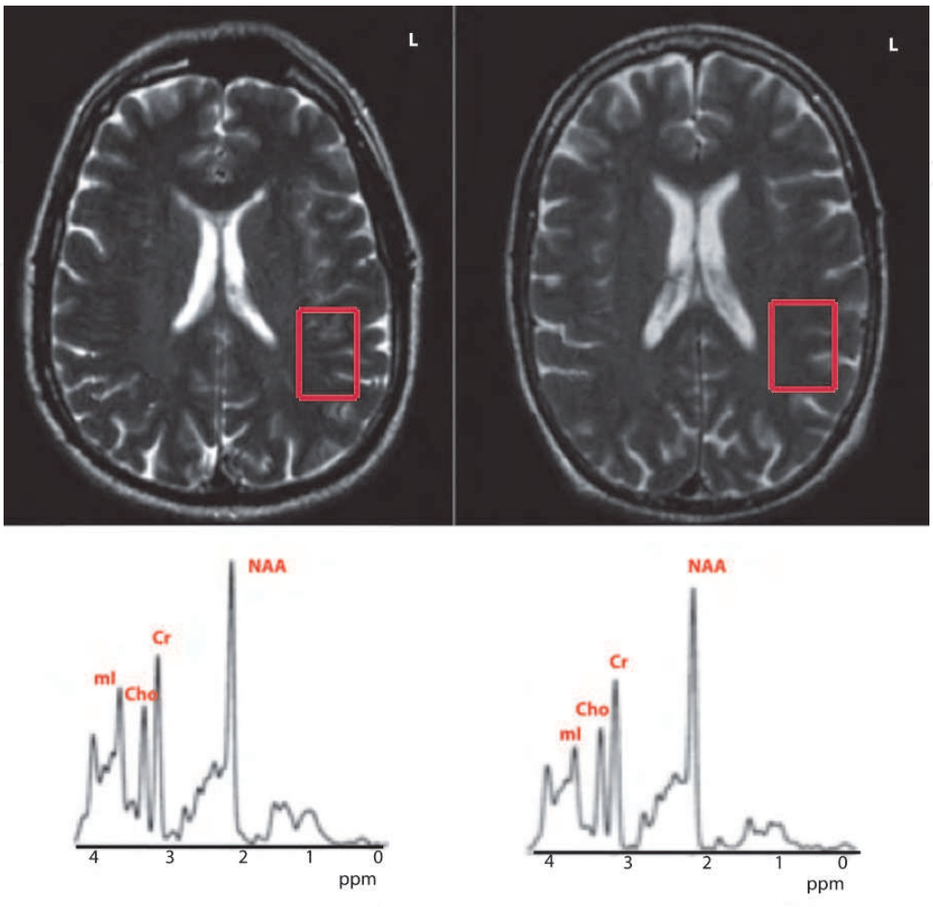

Fig. 3. MRS in Alzheimer Disease
Axial T2-weighted images from an AD patient (L, left) and a healthy control (R, right). These images show the left parietotemporooccipital region where the spectra was acquired, and the results are shown just below. Please note the differences between the two subjects in the mI.

With regards to AD, and from the early nineties, MRS has become a frequently used technique. The typical 1H-MRS includes the following peaks: NAA, Cr/PCr, Cho containing compounds, Glu and mI. Most authors have opted for following up AD progression using voxels in the medial temporal lobe. However Kantarci et al (2002) states that from a biologic standpoint there is evidence from MR imaging, fluorine 18 (18F) fluoro-deoxy- glucose PET, amyloid ligand PET, and fMRI studies that the posterior cingulate gyri (bilaterally) and the inferior precuneate gyri exhibit atrophy, decreased metabolism, amyloid deposition and deactivation early in the course of AD (Whitwell et al, 2007; Petrella et al, 2007; Chetelat et al, 2003). Moreover, the quality and reliability of 1H MR spectra from these voxel locations are superior to those from the medial temporal lobe because of the close proximity of the medial temporal lobe to the skull base, an area susceptible to magnetic artefacts.

Besides of the voxel location, NAA has been considered a prominent candidate for AD investigation and diagnosis since it is localized only in neurons and absent in glial tissue in mature brains (Simmons et al, 1991). Hence NAA is a general marker of neural integrity. The first ever described finding in relation to AD was a decrease in NAA concentration in the brain (Miller et al, 1992), a reduction positively correlated with the density of senile plaques and neurofibrillary tangles (Klunk et al, 1992). Because NAA is a neuronal metabolite, the reduction of NAA levels in patients with AD is the result of loss of neuronal components, neuronal function disruption, or both; these phenomena are strongly associated with increasing neurofibrillary degeneration. On the basis of the correlation between mitochondrial ATP production and NAA level, NAA production within the neuron is thought to be related to mitochondrial function (Bates et al, 1996).

Both Shonk et al (1995b) and Kantarci et al (2000) described bilateral temporoparietal increase of Cr and mI concentrations as well as the mI/NAA ratio in AD. These authors also found significantly elevated mI and Cr concentrations in the parietal region in early AD stages while NAA remained largely unchanged. Based on these findings they suggested mI and Cr abnormalities could be detected with MRS prior to abnormalities in neocortical NAA (Shonk et al, 1995b). Nevertheless, only the mI/NAA ratio was capable of classifying AD and healthy controls without any overlap between the groups (Panertti et al, 1998). Kantarci et al (2002) found a sensibility around 82% and a specificity ranging from 80 to 90% for MRS in classifying AD, clinically defined, and healthy controls.

The observation of an increased mI concentration not coupled with a cortical NAA decrease had already been reported in a group of AD patients with a low MMSE score and, also, in a group of Down's syndrome patients in the pre-dementia phase (Huang et al, 1999). Therefore mI, but not NAA, showed an inverse linear correlation with MMSE scores (Huang et al, 2001).

The most plausible up-to-date explanation for the increased levels of mI in the brain of AD patients is the contribution of the glial component. Glia contains much higher concentrations of mI than neurons (Glanville et al, 1989) and gliosis may cause the increase in mI found in AD patients (Huang et al, 2001). This may suggest that glial proliferation is a sensitive measure of AD before neuronal loss, the latter reflected by NAA (Fig 3).

Shonk and Ross (1995a) had previously supported the aforementioned hypothesis by showing that adults with Down's syndrome exhibited a significant elevation of mI before the onset of dementia without any concomitant reduction in NAA. On the other hand, cholinergic receptors in the CNS are believed to act in part through the phosphoinositide pathway (Honchar, 1990; Kennedy, 1990). Jolles et al (Jolles, 1992) showed a reduced activity of the inositol polyphosphate enzyme phosphatidyinositol kinase and postulated a specific defect in the inositol polyphosphate cascade in AD to such a degree that cholinergic activity could be affected. Ross et al (2005) summarized this evidence proposing that alterations in mI must have consequences for enzyme equilibrium and the metabolite concentrations in the inositol polyphosphate cascade. Accordingly, altered cholinergic sensitivity could be expected.

During the last decade 1H MRS *in vivo* studies have consistently indicated NAA decreases and mI increases in patients with AD and aMCI (Valenzuela and Sachdev, 2001). The strongest association between MRS and anatomopathologic findings was observed when two metabolite ratios were combined to yield the NAA/mI ratio; this result suggests that NAA and mI have complementary roles in predicting AD pathology. As previously said, NAA is located primarily in neuron bodies, axons, and dendrites. Therefore, it is a sensitive

marker for neuronal density or viability. In patients with amnestic MCI mI/Cr ratios are elevated but NAA/Cr ratios are only mildly decreased. These findings suggest that the mI/Cr ratio increase happens earlier than does the decrease in NAA/Cr ratio decrease in AD (Parnetti et al, 1997).

In a recent 1H MRS study, Cho/Cr ratios longitudinally increased in patients with amnestic MCI who progressed to AD (Kantarci et al, 2007). In contrast, Cho/Cr ratios decreased in patients with amnestic MCI who remained stable.

Wang et al (2009) described: a) Hippocampal mI/NAA increases were significantly larger than those in the posterior cingulate area (an area with a recognized relationship in the pathological progression of AD); b) Hippocampal and posterior cingulated mI/NAA together provided valuable discrimination to differentiate AD, MCI and control groups and c) there were significant correlations between mI/NAA in the hippocampus and the posterior cingulate area and MMSE scores. The posterior cingulate area suffered later neuropathological and spectroscopic changes.

A reduced NAA was found in the right hippocampus ($p = 0.01$) in MCI patients while increased mI was reported in the left hippocampus ($p = 0.02$). mI/NAA ratios were higher in both right ($p = 0.03$) and left ($p = 0.01$) hippocampi of MCI subjects (Franczak et al, 2007). Greater mI concentrations have also been found in patients with MCI (Godbolt et al, 2006; Kantarci et al, 2000). Neuropathological studies of MCI have shown the existence of hippocampal damage. This goes along with the hypothesis that MCI is a transitional state between normal aging and AD. A recent study found reductions in NAA/mI ratios in presenilin 1 and amyloid precursor protein mutation carriers who have a nearly 100% risk of developing AD (Godbolt et al, 2006). Metastasio et al (2006) observed a significant a NAA/Cr decrease in the parietal white matter in a group of five patients who developed AD after being diagnosed with MCI. This was replicated by Pilatus et al (2009). Modrego et al (2005) identified the occipital cortex as the most sensitive area for NAA/Cr ratios. To summarize, MI/NAA ratio may be a useful biomarker for diagnosing MCI and it may help to commence early treatment in affected individuals (Franczak et al, 2007).

In AD patients NAA levels may also return to normal within the first 6 weeks of treatment with donepezil (Krishnan et al, 2003). NAA is not just a marker for neuronal function and, possibly, neuronal mitochondrial function, but can also be a surrogate marker to evaluate progression and decline in neuronal integrity during the transition period from MCI to dementia.

Other attempts to evaluate alternative metabolites have been done. Glu and Gln are decreased in the cingulate gyrus in AD patients (Antuono et al, 2001). However, the precise role of glutamate excitotoxicity in the development of MCI and AD remains largely unknown.

In short, and in spite of the difficulties posed by the voxels localization in the mesial temporal lobe, this seems to be the best place to accurately discriminate between MCI and AD as well as measuring MCI progression. The most relevant metabolites in MCI and AD are mI and NAA. They also allow to correctly classify the patients between those two groups and to evaluate their response and treatment and disease progression.

7. Single-photon emission computed tomography (SPECT)

Brain SPECT allows the study of regional cerebral blood flow (rCBF), which correlates at rest with the regional consumption of glucose and reflects neuronal activity. Thus, the rCBF

indirectly reflects neural activity in each brain region, and allows the earlier detection of functional abnormalities, preceding the stage of symptomatic disease.

The tracers currently used in the clinical practice are ^{99m}Tc-Hexamethyl-propylene-amine-oxime (^{99m}Tc-HMPAO), which is considered to be the most reliable SPECT method, and ^{99m}Tc-ethyl cysteinate dimer (^{99}mTc-ECD). They enter cells due to their lipophilic character and remain trapped because of their conversion to hydrophilic compounds. Their incorporation is proportional to rCBF in the first few minutes after injection. Modifications in rCBF after injection do not change the initial distribution of the tracer because of its intracellular trapping (Farid et al, 2011).

Both radiotracers have a similar behaviour, being captured in the brain, with a distribution pattern corresponding to the rCBF (Koyama et al, 1997). Brain SPECT reveals a specific pattern of abnormalities in AD by demonstrating reduced rCBF in the medial temporal, superior temporal, parietal, posterior cingulate cortex, and precuneus before becoming diffuse and affecting the frontal cortex in advanced stages (Farid et al, 2011).

SPECT images represent the topography of physiopathologic changes in AD (Fig 4) and it is a promising diagnostic tool in the early diagnosis and its differentiation from other potentially treated causes of dementia such as normal pressure hydrocephalus or depression (Bartenstein et al, 1997).

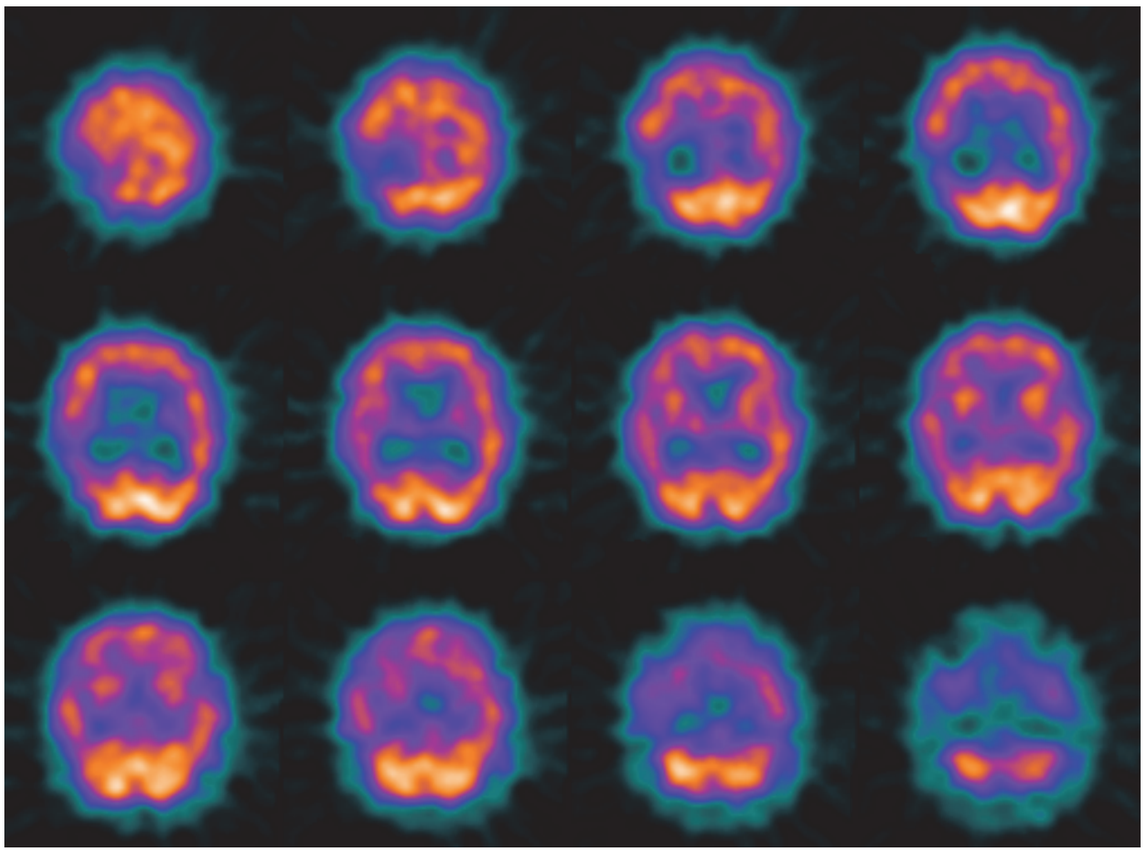

Fig. 4. SPECT in AD. Transversal slices of a 99mTc-ECD SPECT study in a patient with early AD. Bilateral temporal hipoperfusion and assymmetrical parietal hipoperfusion, more evident on the right cortex, can be seen

Haxby et al (1985) were able to link metabolic function, measured with SPECT, with a variety of cognitive and behavioural domains, including memory.

8. Positron emission tomography (PET)

In the last decades there has been a progressive advance in the development of techniques able to explore neurophysiological and neurochemical processes in humans. Positron emission tomography (PET) is a powerful technique allowing the visualization of physiological and biochemical changes both in healthy and ill subjects. This type of unique information may not be available with structural brain imaging techniques. PET has been useful to elaborate the hypothesis of the pathogenesis of AD, in correlating symptoms with their biological markers and in studying individuals at increased risk (Giovacchini et al, 2011).

Glucose is the main energy supply for the brain and its metabolism maintains ion gradients and glutamate turnover, and it is related to neuronal function at rest and during functional activation Its measurement by [^{18}F]-2-fluoro-2-deoxy-D-glucose (^{18}F-FDG) is based on phosphorylation of the tracer by hexokinase, which is the pivotal first step of that metabolic pathway. Measurement of regional cerebral glucose metabolism (rCMRglc) using ^{18}F-FDG PET has become a standard technique in dementia research (Herholz et al, 2007). FDG PET is the approach most efficiently used in AD and MCI diagnosis.

The visualization of metabolic abnormalities using ^{18}F-FDG PET, reveals similar patterns to that of SPECT, with hipoactivity in temporal and parietal neocortex in association with AD, detected either by visual inspection or by conventional quantitative analyses selecting regions of interest (ROI).

PET and SPECT studies using SPM-based image analysis methods have replicated temporoparietal neocortical hypoactivity findings in AD; moreover, these studies have been able to document activity decrements also in the medial temporal region (where the neuropathological process occurs first, with greatest severity and in the posterior cingulate gyrus and precuneus (Matsuda, 2001). That pattern of hypometabolism has been detected even in very early stages of AD (Fig 5) and in subjects at genetic risk for the disorder (Duran et al, 2007).

As AD progresses, the frontal association cortex becomes involved, while cerebellum, striatum, basal ganglia, primary visual, and sensorial and motor cortex remain unaltered (Mosconi, 2005). Hemispherical asymmetries are often observed, especially at early stages of AD and may be attributed to co-morbidity factors (e.g., vascular brain disease) or compensatory mechanisms (e.g., neuroplasticity). This *in vivo* pattern of hypometabolism is found in the majority of clinically diagnosed AD patients and in over 85% pathologically confirmed AD cases (Mosconi et al, 2010).

^{18}F-FDG PET is therefore a useful diagnostic tool to identify the cause of dementia and to have a differential diagnosis with other diseases, and to determine the neurophysiological mechanisms underlying these pathologies. Table 2 shows the characteristic locations of hypometabolism according to different types of dementia. (Montz et al, 2002).

^{18}F-FDG PET is more sensitive than clinical criteria in the detection of AD and in the differential diagnosis with other dementias, reaching values of diagnostic accuracy between 80 and 100%, with sensitivity of 90-96 % and specificity of 67-97% for AD (Gambhir et al, 2001, Knopman et al, 2001 Silverman et al, 1999).

It should be noted that this technique has been helpful in diagnosing AD, irrespective of the degree of cognitive impairment. In fact, abnormal parietotemporal uptake patterns were

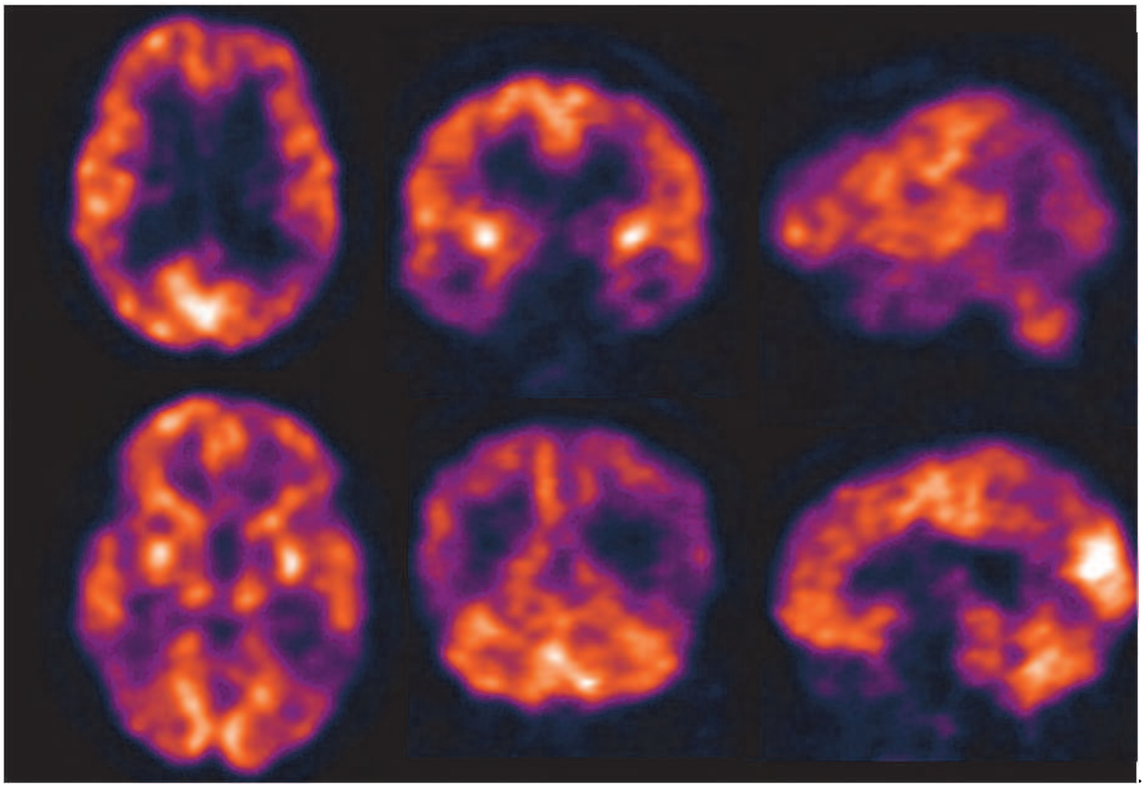

Fig. 5. PET in AD. Transversal, coronal and sagital slices of a cerebral 18F-FDG study of a patient with mild cognitive impairment. Hypometabolism of bilateral temporal and parietal cortex including part of the posterior cingulate gyrus (left dominance) was observed, corresponding to incipient AD.

TYPE OF DEMENTIA	HYPOMETABOLIC BRAIN AREAS
Alzheimer's disease	Parietal and superior/posterior temporal abnormalities; bilateral temporoparietal hypoperfusion (frontal lobe hypoperfusion may happen in conjuncion with temporoparietal hypoperfusion) Earliest changes in medial portion of parietal cortex, posterior cingulated or retrosplenial region
Diffuse Lewy body disease	Temporoparietal associatedwith occipital hypoperfusion
Corticobasal degeneration	Cortex and contralateral thalamus to the affected limb
Progressive supranuclear palsy	Motor/premotor frontal cortex, anterior cyngulate gyrus, hippocampus, basal ganglia and thalamus
Frontal dementia	Frontal, anterior cyngulate gyrus, anterior temporal lobe, hippocampus, basal ganglia and thalamus
Vascular dementia	Irregular pattern of uptake due to strokes
Parkinson's disease	Frontal-temporal-parietal

Table 2. ^{18}F-FDG PET pattern of uptake in different types of dementia

seen on ^{18}F-FDG PET images obtained in asymptomatic members of families in which a familial form of early AD was present. Similarly, asymptomatic subjects with the apolipoprotein ε4 allele were found to have significantly less parietotemporal ^{18}F-FDG uptake than those without this allele. ^{18}F-FDG PET has also proved useful to follow the course of AD patients. A normal PET study indicates that pathologic progression of cognitive impairment during a 3-year follow-up period is unlikely to occur. In another study, investigators were able to predict the clinical course of patients with mild cognitive impairment by using ^{18}F-FDG PET images obtained early in the course of disease (Hammoud et al, 2009).

Few studies have directly compared brain perfusion SPECT and ^{18}F-FDG PET in AD. Ishii et al. in 1999 compared ^{99m}Tc-ECD SPECT images with ^{18}F-FDG PET images in the same ten patients with Alzheimer's disease. ^{99m}Tc-ECD SPECT showed a reduction in parieto-temporal perfusion in 8 of the 10 patients, whereas ^{18}F-FDG PET showed a reduction in temporoparietal metabolism in nine of them. The contrast between the radiotracer uptake in the sensorial and motor areas and that in the parietotemporal region was not as great in the ECD images as it was in the FDG images (Ishii et al, 1999). Messa et al, in 1994, performed ^{99m}Tc-HMPAO SPECT and ^{18}F-FDG PET in patients with mild to moderate AD and in healthy control subjects. They reported that these techniques had similar abilities for visualizing decreased perfusion and metabolism in the temporoparietal cortex and similar diagnostic accuracies (Messa et al, 1994). In 2002, Herholz et al. showed good correlation between ^{18}F-FDG PET and ^{99m}Tc-HMPAO SPECT for detecting changes in the temporoparietal cortex in mild to moderate AD by using voxel-based statistical image analysis (Herholz et al, 2002), although ^{18}F-FDG PET demonstrated a more robust differentiation of patients with AD from healthy volunteers than did SPECT (Matsuda, 2007).

The meta-analysis performed by Yuan et al. in 2008 comparing results of ^{18}F-FDG PET, SPECT and structural MR imaging to predict conversion to AD in patients with mild cognitive impairment, including data from 1112 patients, showed that ^{18}F-FDG PET had moderately better concordance with follow-up results for the prediction of conversion. Approximately 88.9% of the patients with progressive mild cognitive impairment were considered affected by ^{18}F-FDG PET, whereas 84.9% of stable patients had negative ^{18}F-FDG PET (Yuan et al, 2008).

Another method for *in vivo* assessment of the extent of AD is the use of new radiotracers including the amyloid PET tracer Pittsburgh Compound B (^{11}C-PIB) for visualizing fibers Aβ (Morris et al, 2009, Kadir et al, 2011) or 2-(1-{6-[(^{18}F-fluoroethyl)(methyl)amino]-2naphthyl}ethylidene) malononitrile (^{18}F-FDDNP) that has been reported to label not only amyloid but also neurofibrillary tangles (Tolboom et al, 2009), and these methods have generated new possibilities for early diagnosis of brain impairments.

The first attempt to image brain Aβ accumulation in AD was reported by Friedland et al. in 1997 using a monoclonal antibody fragment labelled with ^{99m}Tc for single SPECT. This first attempt failed, but it was fundamental for subsequent efforts (Friedland et al, 1997). The second used PET, and the report of this work was published in 2002 (Shoghi-Jadid et al, 2002). The radiotracer used was ^{18}F-FDDNP but had the disadvantage of a limited experience worldwide (Klunk & Mathis, 2008). The third study of *in vivo* Aβ imaging with ^{11}C-PIB, was reported in 2004 (Klunk et al, 2004).

The quantity of radiotracer measured must be proportional to the amount of Aβ in that area and there must be sufficient signal-to-noise ratio to detect the tracer when levels of Aβ have become clinically significant. There are some published data for PIB demonstrating these

properties both *in vivo* and in post-mortem studies (Klunk et al, 2005, Maeda et al, 2007, Wiley et al, 2009). There is no doubt that the validation of an in-vivo Aβ tracer needs *in-vivo*–post-mortem correlation study in humans. ^{11}C-PIB has the advantage of not showing significant changes over 2 years during clinical AD (Engler et al, 2006).
Several tracers including ^{18}F-BAY94-9172 (Wang et al, 2011) (figure 3), ^{18}F-AV-45, ^{18}F-AH110690, ^{18}F-3'F-PiB, ^{11}C-AZD2995 and ^{11}C-AZD2184 have recently been or soon will be used in multi-centre phase II or phase III trials.
To understand the behaviour of a tracer in neurodegenerative disease, it is important to note that the population should include not only patients with AD or healthy controls. Studies on populations with mild cognitive impairment, early onset familial autosomal dominant AD, Parkinson's disease, Lewy body disease, fronto-temporal dementia, cerebral amyloid angiopathy, prion disease and other atypical dementias and cognitively normal aging contribute to our understanding of Aβ imaging with ^{11}C-PIB. A third principle for acceptance should be widely available of any Aβ imaging tracer.
The leading difference between these radionuclides is their decay 'half-life'. The decay half-live of carbon-11 is 20 min and that of fluorine-18 is 110 min. The main advantage of carbon-11 is that it decays so rapidly that sequential imaging studies in the same patient can be performed on the same day, thus, a ^{11}C-PIB study can be followed by a study using ^{18}F-Fluorodeoxyglucose (FDG). This would require two different days with a fluorine-18-labeled Aβ tracer. However, the 110 min half-life of fluorine-18 allows distribution within a 2–4 h travel radius. Thus, the need for a good fluorine-18 Aβ imaging tracer is mainly a matter of widening the availability. The properties of ^{11}C-PIB appear quite sufficient for imaging Aβ with a carbon-11 tracer, so the current goal is to obtain a fluorine-18 tracer with similar characteristics to those of ^{11}C-PIB (Klunk & Mathis, 2008).
To conclude about these two nuclear medicine brain imaging approaches (SPECT and PET), SPECT with ^{99m}Tc-HMPAO and ^{99m}Tc-ECD and ^{18}F-FDG PET are very useful diagnostic tools for early diagnosis of AD, even in pre-clinical stages. Posterior cingulated hypometabolism, measured with SPECT, may help to predict progression from MCI to AD. Some authors have stated that SPECT can be highly accurate in identifying the type of dementia (Read et al, 1995). The severity of temporoparietal metabolism impairment, measured by FDG PET, is helpful to distinguish those people with a progressive course of their condition from those who have a non-progressive course. This is useful for delivering MCI prognosis. The development of new radiotracers able to demonstrate the presence of Aβ plaques in AD patients, will improve the specificity of those methods. Finally, it is worth mentioning these nuclear medicine neuroimaging methods can serve as surrogate markers in clinical trials of therapeutic agents (Mueller et al, 2005; Teipel et al, 2006).

9. Magnetoencephalography (MEG)

MEG is a non-invasive technique that allows recording the magnetic fields generated by the human brain. MEG provides an excellent temporal resolution up to milliseconds, magnitude orders better than in other methods for measuring cerebral activity, such as CT, MRI, SPECT or PET (Hämäläinen et al, 1993). It generates functional maps with delimitation of cerebral structures in the range of few cm and, even, cubic millimeters. Therefore these functional maps can be organized both temporal and spatially. MEG signal is generated by synchronous oscillations of pyramidal neurons; the MEG detects slightly different features of the simultaneous electromagnetic brain activity and MEG power represents the activity of a given number of neurons discharging synchronously.

Some MEG background activity abnormalities in moderate and severe AD have been observed. AD patients show a decrease of MEG coherence values (Berendse et al, 2000). This biological marker is accompanied by a slowed MEG activity which becomes evident when analyzing the power spectral density of selected frequency bands. In this way, spontaneous MEG activity shows increased slow rhythms and reduced fast activity in AD patients compared with healthy subjects (Berendse et al, 2000; Fernández et al, 2002; Osipova et al, 2005).

It has been proposed that such slowing might be due to an increase in activation of low frequency oscillators rather than slowing of existing sources (Osipova et al, 2005). Fernández et al (2002) analyzed the presence of low frequency magnetic activity (delta and theta bands) associated with AD degeneration. Their results showed that people with AD had a significant increase of this type of frequencies in the temporoparietal area greater in the left hemisphere. Moreover, the values of low frequency were associated with the cognitive and functional state of these patients. Temporoparietal delta activity predicted the scores in mental status scales such as MMSE or CAMCOG. Delta activity in right parietal areas allowed predicting the functional status (FAST stage). Fernández et al (2006C) replicated previous studies stating that temporoparietal low frequency plays a key role in the process that leads from MCI to AD. There is a slow and practically linear low frequency activity from normal aging to dementia where MCI has an intermediate position. This study, once the parietal low frequency was defined as the most relevant feature to characterize these patients, carried a follow-up study of the people with MCI. The next step was to find out if MCI patients with more marked low frequency had more probability to evolve into AD. This group showed that people with MCI and higher parietal delta activity had 3,5 times more chance to develop AD (Fernández et al, 2006A). Broadly speaking, from the perspective of spontaneous MEG activity, one can say that a tendency towards brain activity slowing means a higher risk to develop dementia.

Fernandez et al (2006B) carried out a detailed analysis of spontaneous MEG activity spectral changes where the frequencies spectrum 2-60 Hz was subdivided "microscopically" in 2 Hz bands. The relative power of these micro-bands was then calculated. This approach served to overcome the difficulties in comparing data with previous literature, since there is some variation in establishing the limits of traditional EEG bands. A narrow temporoparietal 20-22 Hz band differentiated clearly the AD group from healthy elderly people and was correlated with the cognitive status.

MCI is an ideal target for this type of studies because the rate to progression to AD in healthy elderly people is about 1-2 % yearly, but in the MCI group this rate is 10-15 %. In fact AD and MCI share some characteristics which make difficult to establish a dividing line between both of them. Essentially anyone diagnosed with MCI will exhibit some cognitive impairments, specifically in the memory domain, that can be measured objectively but allow this patient to carry out a normal lifestyle. Therefore he cannot be diagnosed as suffering from dementia. Because of this fact many authors consider MCI as an intermediate or transitional state between normal aging and AD.

Once MCI was chosen as a target, we did a first study following-up a series of normal elderly people for two years. We realized those patients developing MCI had a MEG activity reduction in medial temporal regions during a memory task compared with those who had normal aging (Maestú et al, 2006). Along this line Poza et al (2007) evaluated the discriminative power of five measures extracted from the MEG power spectrum. The best one of them was the spectral mean frequency (sensitivity = 85%, specificity = 85.71%), thus

confirming the presence of spectral slowing in AD. Spectral changes can also be characterized in terms of ratios between powers in different frequency bands. In a later study Poza et al (2008) showed that a ratio of relative power in fast bands (alpha, beta and gamma) and slow ones (delta, theta) had a 75% sensitivity and a 95% specificity for the same purpose. A comparison of spectral median frequency with various nonlinear measures indicated median frequency was the single best discriminator between AD patients and controls (Hornero et al, 2008).

Another important issue during basal MEG, as well as during basal EEG, is brain complexity. Some authors have found a global decrease in irregularity and complexity in AD during basal (rest) MEG recordings (Poza et al, 2006; Gomez et al, 2006). However, the loss of complexity has been only proven in the high frequencies when a detailed spectral analysis in several frequency bands was performed.(van Cappellen et al, 2003).

Other approaches have focused on analyzing functional connections rather than local abnormalities in AD. A decrease of coherence values in the alpha band (Franciotti et al, 2006) and a general decrease of coherence in all frequency bands (Berendse et al, 2000) have been described. A reduced level of synchronization has also been reported in the upper alpha, beta, and gamma bands of AD patients in comparison with controls suggesting a loss of functional connectivity (Stam et al, 2002). Using resting MEG some authors have shown functional connectivity in AD is characterized by specific changes of long and short distance interactions in several frequency bands (Stam et al, 2006). Decreased levels of functional connectivity point towards the relationship of AD with an abnormal function of the large scale brain networks.

Recently Fernández et al (2010) have shown AD non-linear analysis is characterized by a reduced complexity and connectivity. They calculated Lempel-Ziv complexity (LZC) values and found that MCI patients exhibited intermediary LZC scores between AD patients and healthy controls. A combination of age and posterior LZC scores allowed AD-MCI discrimination whereas no LZC score allowed MCI-healthy controls discrimination. AD patients and controls showed a parallel tendency towards diminished LZC scores as a function of age, but MCI patients did not exhibit such "normal" tendency. Accordingly, anterior LZC scores allowed MCI-healthy controls discrimination for subjects below 75 years. People with MCI exhibited a qualitatively distinct relationship between aging and complexity reduction, with scores higher than controls in older individuals. This fact might be considered a compensatory mechanism in MCI before fully established dementia.

A third type of MEG studies is through brain synchronicity. There is increasing evidence that ubiquously distributed neural systems may communicate through synchronization of their activity. Synchronization here refers to the existence of a consistent relationship between activity patterns of two or more spatially separated neuronal groups. Synchronization can be defined at action potentials level or at oscillatory activity one. Synchronization in different frequency bands has been associated with various cognitive functions and the integration of information in the healthy brain (Stam, 2010).

Using the synchronization likelihood as a measure of functional connectivity, a loss of functional interactions between brain regions in alpha, beta and gamma bands was demonstrated in AD patients (Stam et al, 2002). In the same study coherence analysis did not show any significant differences between AD patients and controls, suggesting that nonlinear coupling might play a role. In a further analysis of the same data, van Cappellen et al (2003) showed that a neural complexity measure was increased in AD in both delta and theta bands, whereas the multichannel correlation dimension was increased in the beta

band; these results argue against a simple concept of 'loss of complexity' in AD and suggest a pattern of decreases as well as increases of functional connectivity in different frequency bands. This pattern was subsequently elucidated in another study showing a loss of mainly long distance left hemisphere functional connectivity in low alpha and beta bands, and an increase in parietal theta and occipito-parietal beta/gamma connectivity in AD patients compared to controls (Stam et al, 2006). The preferential loss of left hemisphere connectivity is interesting because some researchers (Osipova et al, 2003; Fernandez et al, 2006) have suggested a left hemisphere vulnerability rather characteristic. The increased connectivity in occipital and parietal areas is remarkable. Possibly, these changes could also reflect a kind of compensatory mechanism. Coherence analysis of the same data showed a roughly comparable pattern of changes. Furthermore, inter-hemispheric alpha band synchronization likelihood was significantly correlated with the MMSE score, suggesting the functional significance of these resting-state measurements.

A problem of functional connectivity studies based upon correlations between raw EEG or MEG signals is a single source is often picked up by many sensors, giving rise to spurious correlations. This volume conduction problem can be solved by special measures such as the phase lag index, which eliminates possible contributions from common sources, and reflects more accurately true interactions between distributed brain areas, reconstructed functional brain networks (Stam et al, 2007). This approach allows the classification of networks on a scale ranging from completely ordered to completely random. It was shown that in the alpha band brain networks in AD were more random than brain networks of healthy controls. Finally, using a modeling approach, it could be shown that the process that gives rise to abnormal brain networks in AD probably attacks critical connections between networks hubs preferentially.

Lastly, cognitive function studies through magnetic evoked potentials have been widely used both in MCI and AD. The MEG activity pattern during cognitive task is significantly altered (Maestú et al., 2001). A study showed greater MEG parietotemporal activity in the left hemisphere during a memory task in healthy elderly people compared with AD patients. The latter showed a reduction of MEG activity accompanied by an anomalous localization in frontal areas. This activation profile can predict performance in cognitive tests such as the MMSE or CAMCOG, as well as with daily life functional outcomes. Thus a lesser parieto-temporal activation during a memory task is associated o lower scores in cognitive tests, what makes MEG a functional neuroimaging technique useful for diagnosis.

In combining MEG with volumetry data obtained from MRI, we have found a direct relationship between hippocampal atrophy with both an increased magnetic activity of low frequency (Fernández et al, 2003) and a decreased magnetic dipoles during a memory task (Maestú et al, 2003).

A relevant aspect is studying those MEG normal changes which are part of normal aging. We have studied elderly people at different ages and we have found a cortical reorganization as age progresses (Maestú et al., 2004). Besga et al (2010) also found that hippocampal volume reduction allowed the discrimination between AD and MCI patients as compared with controls. The percentage of correct classification was 91.3% when AD patients versus controls were compared, and 83.3% in the case of MCI versus controls. MEG data showed that AD patients exhibit higher theta and delta activity than MCI and controls. Such higher activity was significant in parietal, temporal, and occipital areas. Left parietal theta classified correctly MCI patients (vs controls) in 78.3% of the occasions. Right occipital theta and the left parietal delta allowed correctly discrimination of AD patients (vs controls)

at a 81.8% rate. Left parietal theta discriminated between AD and MCI in 56.6% of the occasions. In addition, the combination of both techniques significantly improved the rate of correct classification, thus indicating that a multidisciplinary perspective of techniques may improve the diagnostic capabilities (Besga et al, 2010).

Osipova et al (2006) used source estimation of ongoing MEG oscillations to detect changes in subjects with MCI. In this study, the distribution of alpha sources did not differ between subjects with MCI and healthy elderly controls. Maestú et al (2006) suggested MEG can provide useful information about the risk of developing MCI. They recorded MEG during a memory task in 15 healthy subjects. Five of these subjects developed MCI after two years. These subjects were characterized by abnormal low frequency activity in the left temporal lobe in the initial recording. The MEG mean frequency power spectrum in MCI subjects was decreased compared to healthy controls, and increased compared to Alzheimer patients (Fernández et al, 2006 A). This suggests once more MCI is, in some respects, an intermediate state between health and AD. Furthermore, an average decrease of 0.17 Hz/year of the mean frequency in healthy subjects was shown. Slowing of MEG in MCI could be related to the risk of developing AD.

10. Conclusion

Along this chapter we have highlighted some issues in relation to MCI. MCI is less known from the brain imaging point of view than AD. The high chance to progress from MCI to AD indicates the need to do more studies on this domain. MRS and those neuroimaging techniques based on neurophysiological measurements, e.g. MEG, can throw light on this area.

Brain imaging techniques have not reached a point yet where they can provide the confirmatory diagnosis of AD. However the likelihood of suspicion of AD can be enhanced by these methods. Table 3 summarizes these brain imaging techniques in AD and MCI.

Neuroimaging technique	**Strengths**	**Limitations**	**Comparison AD-MCI**
CT	Low cost, high availability	Relative poor resolution Poor differentiation grey matter-white matter	Does not add
MRI	Extensive use, high availability	Poor correlation with changes in function and metabolic findings	Volumetry and ROI volumetry can be useful, even more so longitudinally
fMRI	Gives insight into cognitive performance	Conflicting results	Can be useful as well, but results interpretation may be difficult
DTI	Can assess structural connectivity	Utility not proven	AF reductions in aMCI is a robust finding

Neuroimaging technique	Strengths	Limitations	Comparison AD-MCI
Spectroscopy	Provides information about brain chemical content	Utility not proven	NAA and mI may measure progression from MCI to AD
SPECT	Low cost compared with PET	Mediocre resolution Radiation exposure	Limited utility
PET	Can detect metabolic changes in AD	Expensive Lack of availability	Most useful tool to differentiate AD from MCI, so far
PET-amyloid	Detects most specific metabolic change linked to diagnosis	Difficult interpretation as neurometabolic changes may antecede disease	Can be a risk biomarker, but results interpretation may be difficult
MEG	Gives insight into cognitive performance High temporal resolution	Very expensive	Some usefulness for this purpose has been demonstrated

CT = computerized tomography; MRI = magnetic resonance imaging; fMRI = functional magnetic resonance imaging; DTI = diffusion tensor imaging; SPECT = single-photon emission computed tomography; PET = positron emission tomography; MEG = magnetoencephalography; NAA = N-acetyl aspartate; mI = myoinositol; AD = Alzheimer's disease; MCI = mild cognitive impairment; ROI = region of interest

Table 3. Comparison of different brain imaging techniques for AD, with relative advantages and disadvantages, and usefulness for AD-MCI differentiation

Structural MRI is nowadays a standard technique for this purpose, but cheaper techniques, such as CT, may still play a role, even more so in underdeveloped countries. Structural brain imaging, such as CT or MRI, is quite useful for the differential diagnosis of AD with non-neurodegenerative diseases. PET and SPECT are not sufficiently accurate to replace clinical judgment, though they supplement the diagnosis of AD and MCI and help to improve the accuracy of diagnosis. Neuroimaging can be very useful for differentiating AD from frontotemporal dementia as well.

At this moment the rest of the neuroimaging techniques previously mentioned are more used for research than for clinical purposes. Part of the problem is that the brain imaging sensitivities and relative utility of each one of them in AD and MCI are not clearly established. The bulk of neuroimaging research in AD continues to be centered on glucose metabolism, perfusion and tissue content. In the future it is likely the functional neuroimaging techniques will continue to expand. Their refinement will bring greater clarity in the diagnosis of AD as well in the MCI status. Combination of brain images approaches, some of them at least based on molecular issues, such as amyloid imaging, may be promising.

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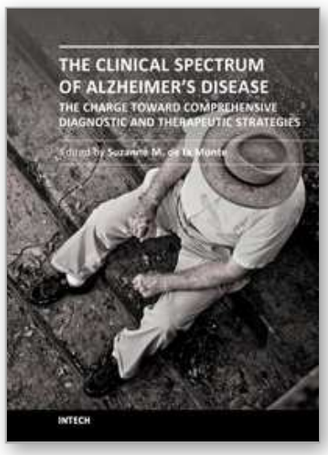

The Clinical Spectrum of Alzheimer's Disease -The Charge Toward Comprehensive Diagnostic and Therapeutic Strategies

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The Clinical Spectrum of Alzheimer's Disease: The Charge Toward Comprehensive Diagnostic and Therapeutic Strategies is highly informative and current. Acknowledged experts in the field critically review both standard and under-appreciated clinical, behavioral, epidemiological, genetic, and neuroimaging attributes of Alzheimer's disease. The collection covers diverse topics of interest to clinicians and researchers alike. Experienced professionals and newcomers to the field will benefit from the read. The strengths and weaknesses of current clinical, non-invasive, neuro-imaging, and biomarker diagnostic approaches are explained. The perspectives give fresh insights into the process of neurodegeneration. Readers will be enlightened by the evidence that the neural circuits damaged by neurodegeneration are much broader than conventionally taught, suggesting that Alzheimer's could be detected at earlier stages of disease by utilizing multi-pronged diagnostic approaches. This book inspires renewed hope that more effective treatments could be developed based upon the expanding list of potential therapeutic targets.

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