in general be understood as a chain process that starts with some physiological changes in the patient, mostly in the brain, that lead to cognitive difficulties which in turn provoke psychological and behavioural changes on the patient.

Regarding the *physiological* symptoms of AD, the best-known changes are the ones evidenced in the brain. It has been found that AD patients' brains contain a huge number of Amyloid plaques and NFT, which are also present in many healthy aged subjects' brains, but in much more moderate amounts. Amyloid plaques refer to the deposits of beta-amyloid (βA) protein fragments, which are accumulated between the neurons and NFT to the deposits of tau protein fragments which are piled up inside the neurons [22]. The accumulation of βA on the brain is considered a necessary but not sufficient condition to produce the clinical symptoms of MCI and dementia [34]. The presence of these plaques and tangles is eventually accompanied by the damage and death of neurons [3], and in fact, one of the most favourable hypothesis about the origin of AD nowadays is the abnormal deposition of these proteins [35–37]. Cerebral hypoperfusion has also been found to be more evident in AD patients than in normal adults, so other hypothesis blaming the vascular and cardiovascular problems to be the cause of this hypoperfusion which in turn could trigger dementia have been developed [38]. Cortical and hippocampal atrophies of the brain are also very well known AD symptoms [9]. Reduction of the volume of the hippocampus is probably the most common pronounced change [26], being a symptom which is already evidenced in the mild stage and which worsens over time. In fact, the authors of [39] affirm that at the mild dementia stage of AD, hippocampal volume is already reduced by 15–30% and in aMCI the volume is reduced by 10–15%. Reduced brain activity and communication between nerve cells has also been found to be an AD symptom, and eye dynamic patters have also been detected to change in these patients.

Cognition-related symptoms are probably the best known in AD. The clinical hallmark and earliest manifestation of AD is episodic memory impairment [40]. Not remembering recently learnt information is the most common symptom, which is discernible from the early stages of the disease. Memory also starts to fail when remembering important dates or events. People in early AD stages may also have difficulties solving daily problems, for example, with number-related tasks as managing finances. Getting confused about the dates, seasons and time, as well as familiar places is another sign of the disease. Vision may also be affected, and the patients may not be able to read, to judge distances or to distinguish colours and contrasts and olfactory dysfunction has also been reported [41]. Communication problems may also arise: patients may suffer from difficulties when expressing themselves, they may repeat things or they may stop in the middle of a conversation without knowing how to continue. Vocabulary loss is also a common sign of the disease, as well as misplacing and not remembering where they left things and thus, losing them. As the disease progresses, this cognitive symptoms become even worse, and the patients start having troubles recognizing people nearby, including family members [22,42]. Reduced prevalence of pain can also be an AD symptom [41].

Progressive deterioration of cognition leads to incoherent *behaviour* and limits the patient's capacity to perform his tasks of everyday life. Therefore, behavioural symptoms of AD are direct consequences of the cognitive changes. AD patients may take much more time than before performing daily activities due to concentration difficulties. Visual problems may lead to many behavioural changes, as, for example, in driving. Due to communication difficulties, the patient may suffer a big change of personality, and a person who has always been very sociable, can be any more motivated to deal with people and have social life. Furthermore, they rely more and more on other people for everyday activities, like eating, bathing or dressing because they may have problems to perform well physically. They may also be unable to walk properly, due to gait and balance dysfunction [41], or to sit by themselves and incontinence and swallowing problems may also arise [22,42].

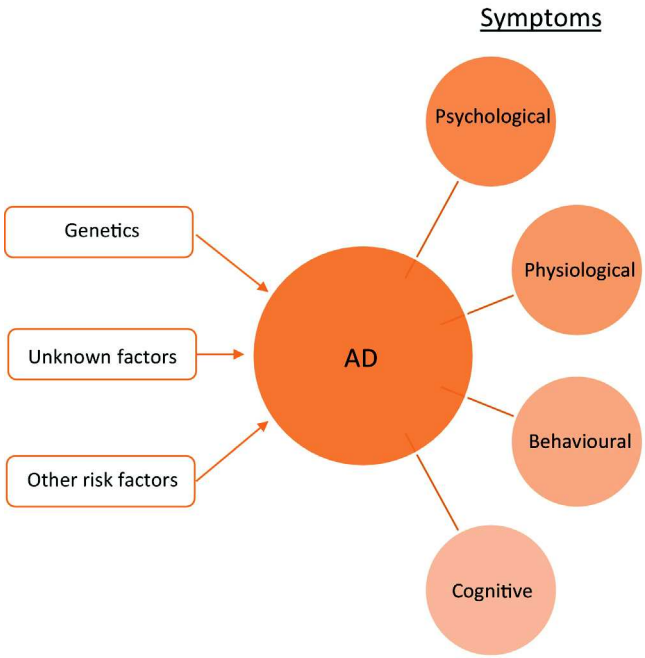

Fig. 2. The multimodal nature of AD.

Psychological symptoms include changes in mood and personality. AD patients can become suspicious because they may think they have been stolen when they lose things, confused when they do not remember the day it is or how they arrived where they are, and depressed, fearful or anxious, because they realize that they do not remember basic things and they do not know how far it can arrive [22]. Depression is the most common psychological symptom in AD. Nevertheless, it is not still clear if depression is really a consequence of AD or a risk factor by itself [43]. Apathy, irritability, agitation, euphoria, disinhibition, delusions and hallucinations are also part of AD symptomatology [41].

3.1. Cognition analysis

AD and MCI levels can be evaluated by means of many tests, among which some are based on the cognitive abilities of the patients. Some examples are the MMSE [44] which is the most frequently used test for AD diagnosis, the Severe Cognitive Impairment Scale [45], the Alzheimer's Disease Assessment Scale – Cognitive [46] which focuses on attention, orientation, language, executive functioning and memory skills, the Neuropsychological Test Battery [47] which includes treatment effects' measurements, the Blessed Test which assesses memory, attention, concentration, and the ability to complete Activities of Daily Living (ADL) and the Severe Impairment Battery [48] which alternatively focuses on measuring the unaffected cognitive functions [49].

Some other tests are the Neurobehavioral Cognitive Status Examination, the Dementia Rating Scale – 2 and the Cambridge Neuropsychological Test Automated Battery [50]. The Rey Auditory Verbal Learning Test and the Category Fluency Test, which test the ability of patients for recalling words, The Trail Making Test which measures the function of brain in general, and other cognitive tasks like the Digit Symbol Substitution Test and the Clock Drawing Test can also help in measuring cognitive functions of AD patients.

This type of neuropsychological tests have been shown to be effective in the assessment of AD. Nevertheless, they present some

drawbacks. The most important one is that the assessment by means of these tests is lengthy and complicated [49]. Furthermore, they are not suitable for all the patients in all the stages of the dementia. Moreover, even if they can measure the dementia state in a certain moment, it can be complicated to early detect AD because they may not show enough sensitivity or because as in many cases, it may be too late when the test is performed.

3.2. Psychological evaluation

As depression is one of the most frequent non-cognitive symptoms in AD (to the extent that a pathogenetic relation between depression and AD has been suggested [51]), psychological evaluation is mainly focused on depression symptoms' measurement.

Geriatric Depression Scale (GDS) is an instrument to detect depression among old adults. Depression can sometimes provoke similar symptoms to those of dementia, even a reversible state called pseudodementia, and therefore, this test allows not to measure the cognitive state of the patients but to see whether depression coexists with AD or another form of dementia or to dismiss any kind of dementia verifying that the symptoms are related to depression without AD [52].

The Montgomery and Åsperg Depression Scale, the Cornell Scale for Depression in Dementia and the Nurses Observation Scale for Geriatric Patients are other possibilities to assess the depression levels in AD patients [51].

Further research is still needed in order to verify if depression is a consequence of dementia, or, on the contrary if it is another risk factor. Once known the relation between both concepts, this kind of psychological assessment could be introduced in a periodical dementia progression test. Nevertheless, psychological evaluation being carried out by means of tests and scales, has the same drawbacks as the cognitive tests, not being suitable for an automatic continuous monitoring system for dementia.

3.3. Physiological signals

Nowadays AD research is mainly based on physiological measurements, making use of both biological signals and imaging methods. Especially the latter are being developed and improved straight off, and this is giving way to AD related physiological changes getting better identified. The volumetric analysis of the brain, which allows to detect atrophy, has been the main objective of imaging, and even if it has been done manually for many years, nowadays, it is evolving and has started to be done automatically, thanks to techniques like the voxel-based morphometry [53,54], tensor-based morphometry [55,56], object-based morphometry [57] and feature-based morphometry [58]. Currently, "neuroimaging plays a central role in the clinical research of cognitive disorders" [59]. Some of the neuroimaging methods are considered for clinical use, namely, Positron Emission Tomography (PET), Computed Tomography (CT) and structural MRI while the others need still further research in order to be accepted.

In this section, the current use and state of the biomedical signals and images that have been considered for AD research is introduced.

3.3.1. CSF

In the recent years, some researches have focused on identifying reliable and valid biomarkers of AD in biofluids [60]. One of these biofluids is the CSF, which is a clear fluid that surrounds the brain and spinal cord mainly for protection. CSF must be obtained by lumbar puncture [61].

CSF "is the only body fluid in direct contact with the extracellular space of the brain and thus biochemical changes due to pathological brain processes are more probable to be reflected in CSF than in other body fluids" [7]. Thus, scientists have made the hypothesis that the accumulation of Aβ plaques on the brain involves a decrease in CSF Aβ42 levels and that this can be already appreciated in the asymptomatic period. CSF tau levels are also known to increase, but it is not clear if this happens after the Aβ accumulation starts [62] or both processes start independently [34], thus, the pathophysiological process of tau might be precedent to the one of Aβ.

Aβ42 is probably the most typical CSF measurement in AD detection, and in the majority of the cases decreased values have been found in AD patients compared to healthy subjects [34]. Aβ40 is also present in the literature but no significant differences have been found for AD patients [63], and sometimes ratios between both Aβ species have also been computed, suggesting that it has potential for both for distinguishing AD patients from healthy subjects and to predict AD in people suffering from MCI [60,63–65]. CSF total tau, as well as some specific tau epitopes (p-tau231, p-tau181 and p-tau199), have been found to increase in AD [34,66] and some researches also affirm its predictability from MCI to AD [60,67]. The ratio of tau-epitopes to Aβ42, in agreement with the precedent results, have also been found to be predictors of AD in MCI patients [67]. Other chemical components like CSF Isoprostanes which have been found to be increased in AD patients even in the preclinical stage [68] and α1-antichymotrypsin, Interleukin-6 and various markers of inflammation which have given ambiguous results [60], even if much less frequently, are also present in the literature. Recently, it has been concluded that the amount of CSF in the hippocampal region is also related to AD [69]. This is probably due to the decreased size of the hippocampus in AD, which leaves space for more CSF.

"Numerous studies on CSF biomarkers for AD have been published during the last years, however frequently providing contradictory and inconclusive results" [34]. Furthermore, many of these biomarkers are not unique to AD disease but to other types of dementia. In addition, this technique is very invasive because CSF must be obtained by lumbar puncture, and thus, it is difficult to use it as a prevention method of the overall population.

3.3.2. Blood tests

Blood samples can be obtained in a less intrusive and less costly way [61] and more frequently than CSF samples, and thus, AD biomarkers on blood have also been searched. More precisely, the blood components plasma and serum have been analysed, as well as platelets [70].

Features extracted from blood samples are similar to the ones extracted from CSF. Aβ42 and Aβ40, which according to the majority of the researches do not show significant differences between AD and healthy subjects [63,71] or give ambiguous results [72,73], Aβ42/Aβ40 ratio which in the study carried out by Koyama et al. [71], at odds with the one performed by Hansson et al. [72], has shown decreased values in AD patients and α1-antichymotrypsin and various markers of inflammation which have not provided evidence about the potential for distinguishing between AD patients and healthy subjects [73].

Isoprostanes and Interleukin-6 have also been extracted from plasma, but they have resulted in the same kind of ambiguous results [60]. In blood platelets, Amyloid Precursor Protein (APP) forms, beta-secretase enzyme (BACE) and alpha-secretase (ADAM 10) have also been measured. Studies have reported that altered values of this biological parameters can be found in AD patients, even in the very early stages of the disease [74,75].

Thus, up to now, it is not clear if blood samples could help in discriminating AD and healthy patients, neither if they could serve as a predictor. The different results obtained could be due to the difficulty to measure Aβ42 in plasma or to the method used for extracting the peptides, as well as to the differences in the

populations studied. Hanson et al. [72] state that whether plasma Aβ concentrations reflect Aβ metabolism in the brain is very unclear and others affirm there is no relation at all [76]. Consequently, blood-based biomarkers of AD have not been still accepted due to the "failure to replicate findings" [61] and to the ambiguous results obtained in different studies. Nevertheless, it would be interesting to research further because blood can be easily obtained in routine tests. Recently, a blood-based diagnosis procedure has been patented but its validity for clinical diagnosis remains to be seen.

3.3.3. CT scans

CT scan is a structural imaging method that uses X-rays to create pictures of cross-sections of the body, achieving with the same dosage of radiation, 100 times more clear images [77] than the regular X-rays. To get this kind of images, specific CT scanners are used.

CT has been used to observe the atrophy of medial temporal regions years ago, but it is not easy to find recent studies about CT as an AD diagnosis source. Varghese et al. affirm that [9] CT is not used as a standard technique for early diagnosis of AD. This could be because other methods have demonstrated to provide greater accuracy, manipulability and precision [60] and because CT is only capable to show late changes in AD [9].

Even if some studies have tried to verify its utility in AD diagnosis [78] due to its simplicity, availability and inexpensiveness compared to other methods such as MRI, nowadays, it is only used to rule out other brain problems, like tumours or haemorrhages, and it "does not have any other role in the early diagnosis of AD" [9].

3.3.4. PET scans

PET imaging is a molecular imaging technique that provides three-dimensional images of a brain at the molecular and cellular level [79]. It consists of injecting or making inhale a substance, called radiotracer, that contains a positron emitter to the patients, detecting the emitted radiation by a scanner and computing a digital image that represents the distribution of the radiotracer in the body [80]. Depending on the chosen radiotracer, different kinds of PET scans can be done. PET Scans are done with PET scanners, but the use of cyclotrons for the preparation of the radiotracers is also necessary, elevating the cost of the equipment.

In AD diagnosis, many different radiotracers have been used for four main purposes: Mainly the ^{11}C-PIB to image the accumulation of the βA plaques on the brain, ^{18}F-FDG to image the glucose consumption of the brain, ^{11}C-PMP, ^{11}C-MP4A, ^{11}C-MP4B, ^{11}C-Nicotine and others to image the neurotransmitter systems of the brain and finally ^{11}C-(R)-PK11195 to image the inflammation in the central nervous system (CNS) which can cause neuronal death [5]. The glucose consumption imaging is based on the idea that as brain mainly uses glucose for energy production, glucose metabolism is closely related to neuronal function, both at rest and during functional activation [20,81].

CAD systems have been developed to try to automatically diagnose AD and MCI. Su et al. [82] proposed a method based on automatically selected ROI features, and classified with a support vector machine (SVM) classifier with a linear kernel, and achieved accuracy rates of up to 91.1% in distinguishing AD from controls, 79.41% with AD and MCI and 78.13% with MCI and controls. They also tested principal component analysis (PCA) and linear discriminant analysis (LDA) based features with both linear and radial basis function (RBF) kernel SVMs and achieved accuracies up to 94.6%, 81% and 79.7% for the same cases as before. Dehghan [83] improved these results combining both FDG and PiB PET scans, and using PCA and SVM algorithms for feature extraction and classification, they achieved 94.12% of accuracy distinguishing AD from healthy controls and 82.05% in the case of MCI and controls. A group of investigators of the University of Granada has published several important works proposing automatic PET based AD diagnosis tools [84–86], reporting high accuracies of up to 98.3% distinguishing AD patients and healthy controls, 77.47% separating CTLs from both AD and MCI patients and 68.79% in classifying MCI patients and controls.

The advantage of PET is that it has the ability to display very mild symptoms [83]. Unfortunately, while theoretically is not a high risk for the patients, it involves exposure to radiation and radioactivity, and, therefore, it is a method that should better be avoided. Furthermore, it is an expensive method and is not highly available, although this fact is changing in recent years [87]. These reasons lead us to believe that PET imaging is not the best-suited method for massive monitoring of the population.

3.3.5. Single photon emission computed tomography (SPECT)

SPECT or perfusion SPECT is a type of radionuclide brain scan that tracks cerebral blood flow (CBF) and measures brain activity [88]. It consists of injecting or making the patient swallow radioactive substances and distinguishing the brain tissues by the radiation emitted by each one of them due to the particular ability of each tissue to absorb this kind of substances. It is a similar method to PET, as both consist on introducing short-lived radionuclides into an amyloid binding molecule, being different the radionuclides used for the two techniques: while PET uses emitting positrons, SPECT needs photons [89]. The two commonest radiotracers used for SPECT are ^{99m}Tc-hexamethylpropyleneamine oxime and ^{99m}Tc-ethylcysteine dimer [90].

SPECT has shown to be a valuable aid for the early diagnosis of AD [91], because it allows to image the hypo-perfusion suffered by AD patients. A correlation between the progression of AD and the loss of cortical CBF in various brain regions [92] has been found with SPECT. A significant correlation was also found between the total tau and phosphorylated tau concentrations in CSF and perfusion in the left parietal cortex [93]. Nevertheless, it is not yet clear in which brain areas this hypoperfusion is most evidenced and thus which one would be the most accurate one for AD diagnosis. Temporoparietal region has been considered practical for the early detection of AD [94], but its sensitivity and specificity is still questioned [91]. Some suggest that posterior cingulate gyri and precunei regions could be more useful [95] while medial temporal lobe (MTL) and hippocampus regions cannot be analysed due to the depth to which they are located [96].

CAD systems have been developed using SPECT images and machine-learning techniques [84,86,94,97,98]. Lopez et al. [84] have been able to distinguish AD patients of Alzheimer's Disease neuroimaging initiative (ADNI) database [99] from CTLs with 96.7% accuracy, using PCA based features of preselected slices of interest and an SVM classifier with a quadratic kernel. Ramirez et al. [97] used SPECT images of 52 subjects, and a methodology based on first and second order image parameter selection and SVM classification. Feature selection techniques yielded a feature vector of only two coefficients, that could still provide a high classification accuracy of 90.38%. These results strongly suggest the potential of such a system to early detect AD.

SPECT shows lower resolution and higher variability [100] than PET, but its radiotracers are cheaper and easier to acquire [101], being probably better suited for longitudinal repetitive studies. Furthermore, SPECT can be carried out by means of a Gamma camera, a device that is already available in most of the greater hospitals [102]. SPECT has also shown the potential to aid distinguishing between AD and other dementias, namely, frontotemporal dementia (FTD), vascular dementia (VD) and dementia with Lewy bodies, as well as between AD patients and healthy controls [90,102]. Nevertheless, the heterogeneity of the results suggest that it should

be combined with other methods. Weih et al. suggested in their review [102] that SPECT could be better used to rule out AD instead of for diagnosing it, as it presents a much higher specificity than accuracy both in distinguishing AD patients from healthy controls and in predicting progression from MCI to AD. The results reported above encourage SPECT-based AD diagnosis research, nonetheless, this can be questioned due to its invasive nature provoked by the use of radiotracers.

3.3.6. Structural MRI

MRI is a non-invasive imaging technique for structural analysis. Shortly, it consists of applying strong magnetic fields to the area that is wanted to image while the different tissues are distinguished thanks to their particular relaxation responses, i.e. the radiofrequency signal emitted by the protons of each tissue, [87] when the magnetization stops. This is done with an MRI scanner.

Structural brain MRI imaging has been widely considered for early detection and diagnosis of AD [28]. This technique can help diagnosing AD in two ways: on one hand, it allows to measure MTL's atrophy, which is closely related to cognition and memory, with very high definition [103,104] and on the other hand, it enables changes on tissue characteristics due to vascular damage to be detected [87]. MTL's atrophy is earliest evidenced in the hippocampus and the entorhinal cortex [28,105–107], followed closely by the parahippocampus and the amygdala [87].

In the last years, the number of longitudinal studies based on MRI images has increased, thanks to databases such as ADNI [99]. This has allowed to better analyse and model the progression of the disease [108] and its effects on individuals' spatiotemporal brain atrophy patterns [109]. Moreover, it has been possible to verify that the brain atrophy in AD patients and in subjects converting from MCI to AD happens much faster than in healthy adults [110,111].

Making use of image processing techniques, automatic diagnosis systems have been developed, achieving satisfactory results distinguishing AD patients from CTLs. Recently, Yepes-Calderón et al. [105] have developed a relatively simple classification system to distinguish between AD, MCI and control patients with MRI and they achieved classifications accuracies of 98.95% when distinguishing AD from control patients. Others have reported accuracies of 92% [30], 89.22% [112], 89% [56], 88.9% [106], 88.49% [28], 87% [26] and 83% [113]. Farzan et al. [114] have achieved comparable results in AD diagnosis from longitudinal MRI data. They used percentage of brain volume changes information of a period of two years, and after applying discriminative analysis (DA) to select the best subset of features, they achieved a classification accuracy of 91.7% in discriminating AD patients from CTL. Others [115] have recently analysed whether it is possible to predict AD conversion from MCI patients using longitudinal MRI data. Apart from affirming this possibility, they found out a difference between male and female patients: while they achieved an accuracy of 61% in males, in females this value raised up to 84%.

As distinguishing control people from those who are developing MCI might be particularly useful in early AD detection, researches have also focused on this. Yepes-Calderón et al. [105] achieved 87.3% of accuracy distinguishing AD and MCI cohorts and 90.64% in the case of MCI and control. MCI and control subjects have also been distinguished in other studies with accuracy rates of 85.4% [28], 84% [56], 81.3% [106] and 78.22% [26].

Currently, MR's role is quite blurry in the early disease stages [11]. Atrophy of the hippocampus can be differenced clearly in AD patients compared to healthy people, but, unfortunately, it may not be so obvious at the early stages, hindering the use of MRI for early detection. Furthermore, brain atrophy is not specific to AD but characteristic of different diseases [87], or the brain can even suffer volume changes due to reasons other than neuronal loss. Nevertheless, some researchers affirm the possibility of predicting and distinguishing between the different stages of AD using automatic MRI analysis and the results reported herein suggest that MRI can contribute positively to an automatic AD diagnosis system, even in its early stages. Furthermore, MRI scanners are highly available nowadays and they are easy to use, so further research is worth.

3.3.7. Functional MRI (fMRI)

Functional MRI is a non-invasive imaging technique for functional analysis that allows to detect some of the abnormalities of AD patients brain's performance [9]. More specifically, fMRI consists of measuring the oxygen concentration of the different brain areas when the subject is developing different tasks or when he is at the rest state for evaluating the default mode network. These way, brain areas involved on each task or at the rest state can be detected [116]. Thus, a blood oxygen level-dependent (BOLD) image contrast that provides an indirect measure of neuronal activity is achieved [59,87]. As in the precedent case, an MRI scanner is needed for this type of imaging.

"The use of fMRI in aging, MCI, and AD populations thus far has been limited to a relatively small number of research groups" [87]. Notwithstanding, fMRI can help diagnosing AD by obtaining information about each brain part's activity. It has been found that AD patients have reduced activity in the MTL [117], particularly in the hippocampus [117–121], but also in the entorhinal cortex [117], while an increased activation has been reported in the prefrontal cortex, probably, due to a compensation mechanism [122,123]. Deactivation in posteromedial cortical areas such as the posterior cingulate and the medial parietal cortex has also been found to be anomalous in AD patients [124,125]. Nevertheless, these anomalies are much less evident in MCI patients, which could complicate the use of fMRI as an early detection component. In some cases, conflicting findings have been done in hippocampal [118,126] and in the MTL [127,128] activation in MCI patients. These differences in results might be due to a compensatory effect, where some brain regions must activate in order to carry out the work that others cannot do anymore. Some researches have suggested that some brain parts follow a U-curve pattern for activation [129]. In the default mode network evaluations, a "significant alteration" has been found in the connectivity between the hippocampus and its surrounding brain areas [130]. Differences in BOLD signals have also been found between AD patients and other dementia sufferers [131–133].

Even if they are fewer than in the case of MRI, some examples of automatic analysis of fMRI images in AD detection can be found in the literature. Khazaee et al. [134] developed an automatic classification system based on SVM and fMRI images, where an accuracy of 97.5% was achieved distinguishing AD from healthy people. Tripoliti et al. have carried out several works [135–137] where an accuracy of 88% was achieved in the same two-class classification problem. Furthermore, they also distinguished elderly CTLs, patients with very mild AD and those with mild AD with 80.5% of accuracy and introducing a fourth class of healthy young people they achieved 87% of accuracy.

The biggest advantages of fMRI are probably its noninvasive and no radioactive nature, allowing its safe utilization [59] in a repetitive manner and thus facilitating longitudinal studies. fMRI offers a relatively high spatial and temporal resolution [9] of the activation map of the brain, but, unfortunately, it is very sensitive to head motion. This could be a problem in people that are in an advanced stage of cognitive impairment, as well as the fact that they can have difficulties in performing the cognitive activities that are needed for the test [87]. Nevertheless, the latter should not be a problem for the early diagnosis of the dementia and furthermore, the resting state methodology can help overcome this obstacle.

3.3.8. Magnetic resonance spectroscopic imaging (MRSI)

MRSI, also known as Chemical Shift Imaging, Spectroscopic Imaging or Multivoxel Spectroscopy (or Multivoxel MRS) [138], is a non-invasive imaging method that can be performed in a standard MRI scanner. Unlike MRI that visualises anatomy in living tissue by only using the signal of water, MRSI makes also use of MRS technology that can detect biochemistry by using signals from organic molecules, allowing *in vivo* detection and measure of concentration of some low molecular weight metabolites [59,138,139]. "This technique is based on the phenomenon of chemical shift to distinguish between various cerebral metabolites, whereby the H^1 signals from the metabolites exhibit slightly different resonant frequencies dependent on their specific chemical environment" [140]. As the chemical shift of a single metabolite is constant, it will always peak at the same frequency [141] and thereby, MRS provides a spectra in which each peak represents a metabolite or group of metabolites. The area under the peak is related to the concentration of the metabolite. These metabolites include myo-Inositol (mI), choline (Cho), N-acetyl aspartate (NAA), creatine (Cr), glutamate and glutamine (Glu) [142].

AD patients have shown metabolite abnormalities like decreased NAA or NAA/Cr levels [143–149], elevated mI/Cr ratio [144,147], increased or decreased Cho/Cr ratio levels depending on the stage of the disease [150] and decreased Glu levels [147–149] in the gray matter (GM). NAA/mI ratio has been found to be useful for distinguishing between AD patients and healthy subjects. In fact, some affirm [141,151,152] that this is the most robust marker of the disease. MRSI could also help in the prediction from MCI to dementia. Some studies have reported lower NAA/Cr [153–157] and higher Cho/Cr [158] levels in several brain regions in MCI patients who developed dementia than stable MCI subjects. Nevertheless, some disagree with these findings [159,160] so further research is needed to verify MRSI's predictability from MCI to AD. Some researches have also affirmed the potential of MRSI to help in distinguishing different types of dementia from AD, such as FTD [161] or subcortical ischemic VD [162,163].

Nevertheless, MRS has some drawbacks. The concentration of metabolites in the body compared to water concentration is small, resulting in low SNR images and long acquisition times [139], which in turn makes this system sensitive to motion artifacts [138]. Furthermore, it provides a low spatial resolution. Consequently, MRS "is little used in the clinical evaluation of subjects with dementia" [164]. Furthermore, for the best of our knowledge, automatic AD diagnosis systems based on MRSI and machine learning techniques have not been reported up to date.

3.3.9. Diffusion tensor imaging (DTI)

DTI is a MRI technique that can provide information about brain tissue microstructure. It can be obtained non-invasively using an ordinary MRI scanner. It takes advantage of the Brownian motion phenomenon suffered by water molecules in human tissues, which makes them collide randomly between them and with other molecules. In pure water, molecules move in all directions isotropically, i.e. with equal probability, but the cell membranes and the large protein molecules of the human tissues limit the rate and the orientation of the water molecules' diffusion, rendering movements an-isotropic [59]. Thus, the microstructure of the human tissues can be inferred from the water molecules' diffusion patterns [165]. In other words, DTI identifies indirectly "the microscopic aspects that provide measures reflecting the patterns in size, orientation and organization of tissue which are supposed precursors to the final stage of macroscopic tissue atrophy" [166,167].

It has been proven that DTI can provide relevant information about a person's cognitive state, being mean-diffusivity (MD) and fractional anisotropy (FA) the main measures used for it [59]. FA has shown significant differences in the cingulum, splenium of the corpus callosum, uncinate fasciculus, superior longitudinal fasciculus and frontal lobes between AD patients and healthy controls, and MD in the hippocampus, splenium of the corpus callosum, parietal lobes and temporal lobes. MD has been found to increase with cognitive performance decline, especially in the temporal structures while FA decreases [168]. The hippocampal area, the posterior cingulate and the corpus callosum have also shown moderate early cognitive dysfunction evidence in DTI images [166,169], which could allow early detection of AD. For this purpose, DTI has shown superior effect sizes compared to volumetric MTL measurements [170]. Some few studies have also shown abnormalities in MD values in healthy subjects at risk of AD [171,172], which could lead to a very early diagnosis when cognitive changes have not yet started.

Machine learning methods have been applied to DTI images in several researches both for automatic MCI and AD diagnosis. O'Dwyer et al. [19] made use of DTI images and an SVM algorithm with an RBF kernel and achieved 92.9% accuracy in distinguishing MCI from control healthy subjects, and a very similar result of 92.785% considering a three class classification problem with aMCI, non-amnesic MCI and control subjects. Wee et al. [173] combined both DTI and fMRI images in order to obtain complementary features related to the white matter (WM) and to the GM respectively. The combination of the two techniques and the SVM algorithm with a linear kernel gave significantly higher classification accuracies distinguishing MCI from healthy control subjects than using each one of the techniques alone. Specifically, 96.3% accuracy was achieved with the combination method, compared to 88.89% accuracy using DTI alone and 70.37% using fMRI alone. Dyrba et al. [174] created a diagnosis methodology for AD emphasizing in its real future application and taking into account the variability that can be found in DTI images taken with different MRI scanners. For that, they made use of DTI taken from 9 different scanners and created a methodology to distinguish AD from control subjects. The best classification accuracy of 83.3% was achieved for the MD information extracted from the images, using an SVM algorithm with RBF kernel. Their work showed that DTI can be robust enough to be incorporated to AD diagnosis systems if the necessary treatments are applied.

DTI has shown to be a very potential tool in the early diagnosis of AD, because it can detect alterations that cannot be detected, for example, by conventional MRI [175]. It still presents some drawbacks, because there is still uncertainty about the best choice of diffusion parameters and about the methods to use to manage crossing fibres [59]. Nevertheless, these obstacles are being overcome, so before long DTI could be accepted as a clinical diagnose tool.

3.3.10. Transcranial Doppler (TCD) ultrasonography

TCD ultrasonography is an imaging technology that has been used to assess cerebral hemodynamics [176], namely, CBF. Tranquart et al. [177] were among the first in measuring CBF using this technology, testing it in rabbits, while Macé et al. [178] have more recently presented a high resolution CBF imaging technique based on the same principle. This method is based on the Doppler effect, and is executed with an "ultrasound probe that sends high-pitched inaudible and invisible sound waves into the body, which "bounce" off of the tissues in varying patterns" [179]. The parameters of these patterns allow to compute the direction and speed of the blood flow. The experience of the operator and the indirect parameters like the depth of the sample volume, the position of the transducer and the direction of the flow allow to assign the received Doppler signal to a specific artery [180].

Studies based on this technology have been carried out in order to verify its potential to detect AD and to predict it. Several findings have been done [181]. Silvestrini et al. [182] found out an

increased carotid intima-media thickness (IMT), which is a parameter of the arterial wall, in AD patients compared to healthy subjects. This increase in IMT could also indicate a higher short-term risk of developing AD or to convert from MCI to AD [183]. A higher degree of carotid atherosclerosis has been found to be correlated the same way with the disease and a higher risk of developing it [184]. The total CBF is also decreased in AD patients [185,186], as well as the cerebrovascular reserve capacity (CVRC) and the mean flow velocity (MFV) [176,180,187,188]. CVRC "is a parameter of cerebrovascular autoregulation describing the ability for vasodilation of cerebral arterioles in setting of low cerebral perfusion pressure" [180]. Decreased CVRC or middle cerebral artery flow velocity could also reveal a higher risk for developing a dementia [189]. The pulsatility index (PI) has been found to increase in AD [176]. A few studies have also focused on cerebral micro-embolization, and have concluded that people suffering from dementia, both AD or VD, are more affected by this effect [190,191].

Despite these findings, for the very best of our understanding, researches aiming to create an automatic early diagnosis system for AD have not yet been reported. Nevertheless, advances have been done in this area developing image processing algorithms to better focus on regions of interest, i.e. the carotid artery wall, in ultrasound images [192].

Vascular impairment can be detected by several imaging methods like PET or SPECT, but ultrasonography can be a non-invasive and cheaper alternative, thus no radiation or injections are needed. Unfortunately, ultrasonography has also some drawbacks. Mistakes can be done in the identification of individual vessels and in the estimation of blood velocity due to the angle between the vessel and the ultrasonic beam [180]. Nowadays, colour-coded duplex ultrasonography might overcome some of these drawbacks, but it offers lower performance for long monitoring. Furthermore, even if some researches suggest the possibility of using ultrasonography to distinguish between AD's symptoms from other dementias such as the VaD [193], this is not still possible [181]. Even worse, given that the relationship between vascular degeneration and dementia is not clear, it cannot even be known if this technique could really serve as a diagnosis method. Nowadays, it can just serve for monitoring the vascular system's state for AD prevention.

3.3.11. Electroencephalogram (EEG)

EEGs are called to the recordings of the electric field of the scalp caused by the electrical signals exchanged between neurons [4]. Thus, they reflect the communication activity between nerve cells, which is of great importance in neurological diseases like AD.

Studies have shown that EEG may have the potential for an early AD detection. It has been widely accepted that at least 3 types of changes occur in AD patients' EEG signals: they slow down (i.e. the power of low frequencies is found to be increased while the power of the high frequencies is decreased), their complexity, which is the measure of the number of different patterns in the signal [4], is reduced and synchrony or correlation between EEG signals of the different parts of the brain is reduced [4,194].

In the recent years, EEG has shown promising results in AD and MCI detection. An Italian group of researchers have developed automatic EEG based diagnosis methods, using an algorithm called IFAST, which is based on Artificial Neural Networks (ANN). IFAST consists in synthesizing EEG data by computing spatial features of EEGs that are represented by some ANN based connection parameters [195]. Using these techniques they have achieved 93.46% accuracy separating MCI from healthy elderly [196] and 92.33% distinguishing AD patients from MCI [197]. They have also shown the validity of the IFAST method to predict conversion from aMCI to AD with high accuracy (85.98%) in a 1-year follow-up study [195]. Recently, they have improved their method [198] by using a feature extraction technique called MS-ROM and a combination of some classification algorithms, namely, k-nearest neighbours, naïve Bayes and quadratic discriminant classifier. They have reported very satisfactory results: an average of 93.48% for AD detection, 97.88% for MCI detection and 94.05% for AD vs MCI discrimination. Trambaiolli et al. [199] have used SVM to classify healthy people and probable AD patients, using EEG signals, and 79.9% accuracy was achieved. Individual models were also tested by analysing for each one of the subjects the ratio between the number of correctly classified EEG epochs and the total number of EEG epochs, resulting in higher accuracies of up to 87%. In the study carried out by McBride et al. [35], EEG signals have been used to discriminate control, MCI and AD patients. Spectral and complexity features were used for three SVM classifiers, that aimed to solve three two class classification problems: control vs MCI, control vs AD and MCI vs AD. A majority voting system was used to solve the overall classification problem based on the results of the previous classifiers. 91.4%, 84.4% and 89.9% of accuracy was achieved in the first, second and third two class classification problems respectively, and an overall classification accuracy of 82.6% on the classification of the three classes. Recently, another very promising method based on EEG synchronization analysis have been proposed for the early diagnosis of AD [200].

Many researchers [1,4] support the use of EEG for a longitudinal monitoring of changes in the brain, due to the cheap and non-invasive nature of this method and because of the ease with which anybody can take samples without the need of going to a medical facility each time. It is a "simple, relatively inexpensive and potentially mobile brain imaging technology" [201] but further research is needed for EEG to be included in a clinical AD diagnosis.

3.3.12. Magnetoencephalogram (MEG)

MEG is a non-invasive medical imaging technology. MEG identifies the brain activity by measuring the magnetic field created by the electric current flowing within the neurons. Thus, measurements follow a similar principle to the ones obtained by EEG because both measure the same sources of brain activity. A MEG scanner is needed for this imaging purpose.

MEG findings related to AD are similar to those of EEG. Increased delta and theta activity [202–205] in frontal and central areas [206] and decreased alpha activity in posterior and temporal regions [206] has been reported in several pieces of research, i.e. slower signals. A generalized loss of functional interactions (i.e. decreased synchrony) has also been found [202,207,208]. People with MCI have also been investigated with MEG, verifying that their symptoms are somewhere between those of AD and controls [203,209,210].

MEG has been less studied than EEG, probably, because the results obtained up to date with this method suggest that it has a lower discriminative potential than EEG. Gómez et al. have highly contributed to the use of these signals on AD diagnosis, publishing several researches based on it. They have analysed several MEG features' ability to discriminate between AD patients and healthy controls, including Sample Entropy (SampEn) and Lempel-Ziv complexity (LZC) [211,212], Shannon spectral entropy (SSE), approximate entropy (ApEn), Higuchi's fractal dimension (HFD) [213], Maragos and Sun's fractal dimension (MSFD) and Cross-approximate entropy (Cross-ApEn) [214]. They have concluded that MEG really has the potential to discriminate between these two groups, as they have achieved accuracies of 70.83% using the Cross-ApEn, 77.42% with SSE, 87.8% in the case of HFD and 85.37% with SampEn and LZC parameters introduced to an ANFIS classifier. Nevertheless, for the best of our knowledge, no research has analysed if the results remain so high when an MCI group is considered, which could be interesting to analyse the predictability to AD and early detection potential of MEG signals.

MEG can be done without placing uncomfortable electrodes and it is less affected by conductivity issues related to the skull and scalp [215], they do not require a reference, they are less affected by volume conduction, and furthermore, they can obtain more sensitive measurements of the cortical activity than scalp EEG. The disadvantage of MEG is the interference that Earth's magnetic field or the electrical devices can introduce, so measurements must be done in a heavily shielded room with all the electrical devices around switched off, which complicates its use as part of a global routine monitoring system. Furthermore, results show that the accuracy obtained up to date with MEG doesn't reach the one obtained by EEGs.

3.3.13. Eye dynamics

It has been hypothesized that "the pattern of AD-specific neurodegeneration may affect neural circuitry of the eye movement system in a unique manner that allows the clinical differentiation of AD from other cognitive disorders" [216]. In order to verify this hypothesis, eye movements of AD patients have been compared to those of healthy subjects in many studies and effectively, it has been proven that AD patients suffer from changes in oculomotor and pupillary functions [217]. More precisely, changes in saccades, smooth pursuit function and in the pupillary response have been found by some researchers. Saccades are "rapid, conjugate movements of the eyes, which serve to orient the high acuity foveal region of the retina onto a specific region of visual space" [218]. Saccadic movements can be distinguished into three different types: prosaccades, which are eye movements towards a target, antisaccades, which are movements in the opposite direction of a target, and finally, microsaccades and saccadic intrusions, which are minuscule eye movements that happen during fixation. It is thought that saccades are of particular interest because they are very related to attention and thus, they are likely to be disturbed by cognitive impairments associated with neurodegenerative disorders such as AD, as well as by dysfunctions related purely to oculomotor execution [219]. All these behaviours can be measured easily and in a non-invasive way in a laboratory, making the patients carry out specific tasks like the reflexive paradigm, the memory-guided paradigm [219], the gap/overlap task or the antisaccade task [220] while their eyes are being tracked by cameras or infrared systems [221] and image processing techniques. Reading tasks have also been used [222].

Some researches have revealed that AD patients show higher latency than healthy subjects when starting prosaccades [223–226], that the velocity of these prosaccades is lower [226] and that the accuracy when reaching the target also worsens [220]. Antisaccades have also been analysed in some researches. It has been found that in this case too, latency increases in AD patients compared to healthy people, and that the number of incorrect saccades toward the target increases while the number of corrections after the error decreases [220,223]. Peltsch et al. [227] compared aMCI, mild AD and healthy people's antisaccades concluding that aMCI and mild AD patients showed very similar performance in the antisaccade task. Related to AD patients' microsaccades and saccadic intrusions, it has been found that they are much more oblique, frequent and greater in amplitude [223] than healthy peoples' ones. Hence, their gaze-fixation is much more unstable. Nevertheless, disagreements exist with these results. Some have not found differences in speed and accuracy of AD patients' saccadic movements [224], neither in gap tests' results. Smooth pursuits are slower eye movements that serve to keep an object foveated if it moves across our field of vision [218]. It has been found that AD patients' smooth pursuit function is affected in a similar way as saccadic functions, i.e. they show increased latency and decreased velocity, velocity gain (pursuit velocity/target velocity) and initial acceleration. They also tend to anticipate to the targets' movement, resulting in more compensatory saccades. Pupillary responses have also been studied by some researches, and they have found out that these responses show a greater latency, and smaller amplitude, velocity and acceleration in AD patients that in healthy people [228].

Despite the power of the eye dynamics' for AD detection, no many researchers have tried to develop an automatic AD detection system using eye movement features and machine learning techniques. Lagun et al. [221] are about the only ones taking advantage of these biomarkers for AD recognition. They used the visual paired comparison task, which consists on identifying the eye movement pattern of the patients while introducing new visual stimulus. It has been seen that control patients spend 70% of the time looking at the new stimulus whereas MCI patients spend the same time looking at the old and new pictures, suggesting that they are not familiarized with anyone of them [229]. They used these and other eye dynamics' features and an SVM classifier, achieving an accuracy of 86.9% distinguishing between MCI and control patients.

The problem with these measurements is that these abnormalities are not always present in AD patients and furthermore, they are not unique to them [219]. Moreover, it is not clear if MCI patients also show signs of these abnormalities because while some refuse this fact [224], others have found some evidences [220,225]. Crutcher et al. [229] have also found that some MCI preferred the new images the same as the control patients, demonstrating the variability between patients' patterns. Consequently, further research is needed to verify if they might be used both as AD biomarkers and as predictors in the early stages.

3.3.14. Summary

The great effort being made in Alzheimer's research in the last years has allowed to identify many AD-related physiological biomarkers so that the AD diagnosis is becoming more and more accurate. Table 1 summarizes the physiological biomarkers of AD that have been found in the literature.

As it has been seen in this section, many types of signal processing techniques and imaging modalities have been tested so as to find out the best signals and features that can be used to diagnose AD automatically, or at least to assist the specialist in

Table 1
Physiological AD biomarkers of the literature.

Method	Biomarkers
CSF	Aβ42 ↓, Aβ40, Aβ42/Aβ40 ↓, total tau ↑, p-tau231 ↑, p-tau181 ↑, p-tau199 ↑, [p-tau231, p-tau181, p-tau199]/Aβ42 ↑, Isoprostanes ↑, α1-antichymotrypsin, Interleukin-6, markers of inflammation, amount of CSF in the hippocampus ↑
Blood	Aβ42, Aβ40, Aβ42/Aβ40, α1-antichymotrypsin, various markers of inflammation, Isprostanes and Interleukin-6, APP, ADAM 10, BACE
CT	Brain problems other than dementia
MRI	MTL's atrophy, vascular damage
fMRI	Activity in the MTL ↓, prefrontal cortex ↑, capacity of deactivation in PMC ↓
MRSI	NAA ↓, NAA/Cr↓, mI/Cr↑, Cho/Cr↑, Glu ↓, NAA/mI ↓
TCD	Carotid IMT ↑, total CBF ↓, CVRC ↓, MFV↓, PI ↑, cerebral microenbolization ↑
DTI	MD↑, FA↓
PET	β-Amyloid plaques ↑, glucose consumption ↑, anomalies in neurotransmitter systems, inflammation in the CNS ↑
SPECT	CBF ↓,CSF ↑, perfusion ↓
MEG/EEG	Delta and theta activity ↑, alpha activity ↓, complexity ↓, synchrony↓
Eye dyn.	Prosaccades' and antisaccades' latency ↑, velocity ↓ and accuracy ↓, no. of incorrect saccades ↑, no. of corrections ↓, obliquity↑, frequency↑ and amplitude↑ of microsaccades and saccadic intrusions, gaze-fixations' stability ↓, anomalies in smooth pursuit function, pupillary responses' latency↑, amplitude↓, velocity↓ and acceleration↓

the hard decision of the diagnosis. Table 2 shows the signals and imaging modalities used in the literature with their respective features. Nevertheless, much less work has been done related to the automatic early diagnosis of MCI and AD, which is the key for the prevention of dementia's progression.

Table 3 shows the best accuracies achieved in the state of the art distinguishing AD patients from CTLs using physiological signals and images, while Table 4 is its equivalent for MCI diagnosis and Table 5 for MCI and AD discrimination. The results for the three classification problems are very promising. It is evident that

Table 2
Physiological features used in the literature.

Method	References	Features	Parameters
MRI	[135–137,113,106,28,56, 26,112,30,105]	GM voxel values	Mean, SD
		GM volume	Voxel location, PCA eigenbrains, PLS[a]-brains, sICA basis functions
		WM volume	PCA eigenbrains, PLS-brains
		GM + WM volume	PCA eigenbrains, PLS-brains
		Hippocampal volume	Total volume, CHF (visual features), CSF volume
		Total brain volume	PCA eigenbrains, GM volume/total volume
		Cortical thickness	Average within a ROI
		MBL[b] features	Coordinates
		Atrophic voxels	average Jacobian within a ROI
		MTL volume	Grey-level data, volume change estimation
		35 ROIs	Structural thickness, contour area, volume, structural curvature
fMRI	[134–137,173]	Head motion	Path length (see [230])
		Activation patterns	No. of activated voxels, max *z*-score, size of the cluster where the max *z*-score belongs to, no. of significant clusters, % of activated regions that belong to a ROI, total activation of ROIs, atlas based ROIs' clustering coefficients of functional connectivity networks of several frequency sub-bands
		BOLD response	Amplitude, undershoot and transit time
		CBF	Amplitude
		Venous volume	Amplitude
		Vascular signal	Amplitude
		DeoxyHb signal	Amplitude
		Brain network graph	Degree, participation coefficient, betweenness centrality, local efficiency, local/global efficiency
DTI	[174,19,173]	FA	Mean
		MD	Mean
		Axial diffusion	Mean
		Radial diffusion	Mean
		Fibre connectivity network	
PET	[82–86]	Intensity of the whole brain (VAF[c])	Eigenbrains (PCA), ICA based features, LDA projections, 22 ROIs, average of 48 ROIs
		Intensity of VOI[d]	Eigenbrains (PCA)
SPECT	[97,86,84]	First order histogram	Mean, variance, entropy
		Co-occurrence matrix	Angular second moment, contrast, inverse difference moment, entropy, correlation
		SOIs (slices of interest)	Eigenbrains (PCA)
		Voxels of interest	Eigenbrains (PCA)
		VOIs	NMSE[e] features
EEG	[196,35,199,197]	Delta, theta, alpha, beta and gamma bands' spectrum	power densities, total spectral power, specific spectral power ratios (see [35]), coherence between several combinations of pairs of electrodes, peak alpha band, spectral peaks of biauricular references, spectral peaks of bipolar references, median frequency, spectral entropy
		Temporal signals of Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2	Connection weights derived from IFAST methodology, activity, mobility, complexity, SampEn, LZC
		First derivative	Total spectral power, peak alpha band frequency, median frequency, spectral entropy, SampEn, LZC
MEG	[211–214]	Temporal signals	SampEn, LZC, ApEn, MSFD, Higuchi's fractal dimension (HFD), cross-ApEn
		Spectrum	SSE
Eye dyn.	[221,229]	Pupil diameter	SD/mean during tests and outside them, pupil dilatation in tests $((mean_{test} - mean_{fam})/mean_{test})$
		Fixations	Median duration, mean re-fixation depth, total duration, total no. of fixations, total fixation time, novelty preference
		Saccades	Orientation

[a] Partial Least Squares.
[b] Manifold-based learning.
[c] Voxels-as-features.
[d] Voxels of interest.
[e] Normalized mean square error.

Table 3
Accuracy rates reported in the literature for AD vs CTL discrimination.

Reference	Signal	Accuracy (%)
[105]	MRI	98.95
[86]	PET	98.3
[94]	SPECT	98.3
[40]	Speech	97.7
[134]	fMRI	97.5
[98]	SPECT	96.91
[35]	EEG	96.9
[84]	SPECT	96.7
[82]	PET	94.6
[83]	PET	94.12

Table 4
Accuracy rates reported in the literature for MCI vs CTL discrimination.

Reference	Signal	Accuracy (%)
[198]	EEG	97.88
[35]	EEG	96.8
[173]	DTI + fMRI	96.3
[196]	EEG	93.48
[19]	DTI	92.9
[105]	MRI	90.64
[221]	Eye dyn.	87
[28]	MRI	85.4
[56]	MRI	84
[83]	PET	82.05

Table 5
Accuracy rates reported in the literature for MCI vs AD discrimination.

Reference	Signal	Accuracy (%)
[198]	EEG	94.05
[19]	DTI	92.785
[136]	fMRI	93
[197]	EEG	92.33
[35]	EEG	90.9
[105]	MRI	87.3
[135]	fMRI + MRI	87
[195]	EEG	85.98
[82]	PET	81
[115]	MRI	83.78[a]
[28]	MRI	78.92

[a] In females.

diagnostic rates in real life using these methods would not be as high as the ones that have been achieved in laboratory experiments because in real life there is much more variety of diseases, and probably, also much more variation in the progression of dementia. However, these results verify that automatic signal and image processing methods have the potential for both AD diagnosis and early AD diagnosis (or MCI) when they are combined with other methods.

Nonetheless, most of the analysed neuroimaging methods still lack to have established validity, sensitivity, specificity, predictive value, repeatability and concordance [231] to have real diagnostic value. Variability in participant selection, methodological inconsistency and use of different acquisition protocols between the different researches are the main causes for this problem [59]. Thereby, further research is required in order to overcome these barriers and establish a valid early diagnosis method based on physiological data.

3.4. Behavioural responses

Although behavioural changes are not less important than physiological ones, they have been much less considered in AD detection research. Some tests and scales have been developed in order to assess patients' autonomy to carry out everyday activities, but much less has been done towards an automatic detection system. The following lines sum up the behavioural assessment methods for AD patients.

3.4.1. General behaviour assessment tests

Behavioural changes suffered by AD patients might be measured by means of questionnaires or tests. These tools may help the patient himself and his relatives to take conscience of the real state of the disease. Tests like the Behavioural Pathology in AD Rating Scale (BEHAVE-AD) [232], the Brief Psychiatric Rating Scale [233], the Behavior Rating Scale for Dementia of the Consortium to Establish a Registry for AD [234], Neuropsychiatric Inventory (NPI) [50] and the Dementia Behaviour Disturbance Scale [235] are questionnaires used to measure the behavioural abnormalities that the AD patients can undergo [49].

Nevertheless, as do all assessments based on questionnaires, they have some drawbacks, including the so common belated diagnosis.

3.4.2. ADL scales

Tests with the main objective of measuring the progress of the dementias by analysing the abilities of the patients for carrying out typical daily activities with normality have been designed. These tests offer additional information to the one given by cognitive tests, because even if a patient has achieved quite encouraging results, he may have problems integrating visual, motor and cognitive skills, making him perform poorly in ADLs. Often, the real state of the dementia can be better assessed and the level of support needed can be much better understood seeing them in action and recording the level of cognitive support required to complete a certain task successfully [236]. Hence, ADLs can be assessed both by means of questionnaires and by specifically designed tasks.

Some tests are based on the most basic activities (ADL), like feeding, walking or dressing, while others measure the abilities for more complex tasks, called instrumental activities (IADL) [49]. Examples of IADL are cooking, tasks which involve the use of money, etc. Katz Index of ADL [237] and the ADCS-ADL 19 [238] test measure the former kind of activities while the ADCS-ADL 23 [238] is suited for the IADL activities. Other questionnaires and interviews like the Disability Assessment for Dementia [239], Interview for Deterioration in Daily Living Activities in Dementia [240] or the Functional Autonomy Measurement System [241] also serve to measure the behaviour regarding the ADL activities.

Among the specific tasks that allow to evaluate the abilities of the patient *in vivo*, the most well known is probably the kitchen task assessment [236]. It is a functional measure that aims to evaluate the processing skills of initiation, organization, inclusion of all steps, sequencing, safety and judgement, and completion of a cooking task for measuring the cognitive aspects of performance by means of behaviour.

3.4.3. Smart homes

A smart home is a regular home that has been augmented with various types of sensors and actuators [242], being its main objective to overcome the cognitive disorders of people to enhance their autonomy [243].

Sensorized devices and environments allow to capture the actions of the residents while actuators can serve for automation or for providing comfort, making tasks easier or finishing the tasks that have not been accomplished by the patients, for example, for security reasons (turn off the oven after a certain time). Prompts or suggestions can also be made to recall to the patients how to continue an interrupted task and to provide them punctual assistance when needed [244]. All these actions should be carried out in a non-intrusive [245] and transparent way, respecting the privacy of the patients, to make it easier for adults to accept this technology

in their daily life. Hence, monitoring systems such as video cameras are not desirable and the selected system should not interfere at all with the normal activities of the patients.

Even if specialized institutions where caregivers are available 24 hours a day exist, both seniors with dementia and their family members normally prefer the patients to be at home as long as possible [244]. Governments also prefer this option due to economical [246] and social reasons. Because of these reasons, smart homes and ambient intelligence (AmI) technology are being increasingly used in order to give assistance to elderly who suffer from dementia or cognitive impairment, to help them accomplish their ADL successfully and to reduce workload to the caregivers. For this purpose, it is necessary to predict these peoples' actions, and therefore, to learn their frequent behaviour patterns [247]. Learning these patterns can also be useful to detect abnormal behaviours [245] and to ease AD diagnosis.

Smart home projects aimed at assisted living both for demented and non-demented elderly currently exist [242] in Europe (Grenoble Health Smart Home [248]) and beyond (CASAS [249], DOMUS [250], MavHome [251]).

Smart homes have been considered as a possibility for MCI detection by a few researchers. Some biomarkers have been found, indicating that this technology could be successfully used in early AD detection. Suzuki et al. [252] have placed infra-red sensors in a smart home for monitoring ADL with an emphasis on people's sleep patterns. More precisely, the number of outings, sleep duration, sleep interruptions and sleep rhythm were measured, and it was concluded that MCI patients went out of home with less frequency and had a shorter sleep time. Wadley et al. [253] have measured the performance of healthy people and MCI patients carrying out ADLs like using the telephone, locating nutrition information on food labels, dealing with money, grocery shopping or medication managing and have observed that it took significantly longer for MCI patients to complete the tasks. Hayes et al. [254] also measured healthy people's and MCI patients' behaviour patterns in smart homes, including walking speed and measures of daily activities. Several markers were found in these case: the coefficient of variation in the median walking times of a week showed to be twice as high in the MCI group compared to the healthy group, the time spent out of home was also less for the MCI group than for the healthy group and the day-to-day pattern of activity of MCI subjects was more variable than for healthy subjects. Furthermore, MCI subjects had longer walking activities in the evening while this was not true for healthy subjects. Akl et al. [255] have recently published a research in where behavioural data of elderly acquired in a real-world experiment conducted in a smart-home was used. Walking speeds, number of walks, number of outings and daily activity were monitored and used to distinguish between cognitively intact people and MCI patients. They achieved an area under the ROC curve of 0.97 and an area under the precision-recall curve of 0.93 using a time window of 24 weeks, proving that smart environments can be really useful to successfully collect relevant data and when they are combined with machine learning algorithms, to quite accurately detect onset of dementia. Researchers from the Washington State University also confirmed this hypothesis [256]. In this case, sensor data collected from 18 real-world smart homes with older adult residents during two years was used. Support vector regression confirmed a statistically significant correlation of 0.72 between processed sensor data and cognitive assessment scores, making possible a prediction of cognitive impairment using only behavioural data. Besides, an accuracy of 71.75% was achieved when classifying this data into two groups with different cognitive scores using SVM.

Smart homes offer the possibility to properly interpret the information given by the sensors using algorithms to recognise ADL [257,258], to learn behavioural patterns [247,259,260] and to detect anomalies [261–263].

Thus, seen that these behavioural differences can be detectable by AmI environments, algorithms that allow to detect subtle behavioural changes [247], and therefore, to detect when the adult is trespassing the limits from healthy to MCI group or from MCI to AD group, have been developed.

Other researchers have focused their work into the development of services or improvements on smart homes to better assist and help already diagnosed people with AD or some other dementia [244,264].

3.4.4. Gait monitoring

As seen in the precedent section, smart homes can be used, among other things, to monitor walking activity of the demented elderly. Nevertheless, parameters such as walking speed may not be accurate enough to predict dementia. Gait monitoring takes into account the manner of walking of the person, where much more parameters apart from speed can be analysed. It has been recently found that cognitive functioning and gait are closely related, so gait should not be longer considered a simple motor activity that is independent from cognition but as a complex cognitive task [265]. This hypothesis has been reinforced by dual-task tests [266]. This relationship is achieving more and more importance, and scientists are recently focusing on gait analysis for early AD diagnosis.

Gait monitoring can be carried out using an electronic walkway or force platforms placed on the floor, using cameras and image processing algorithms or by means of wearable sensors like force sensors, accelerometers, gyroscopes, extensometers, inclinometers, goniometers, active markers or electromyography [267].

Changes in gait behaviour have been reported in AD. Decreased velocity and step length, static and dynamic postural instability, and hesitation in starting and in turning and a widened base have already be found. Nonetheless, all these symptoms are part of a cautious walking, and they can also be found in normal ageing elderly. Scherder et al. [268] reported that AD patients differ from the healthy elderly in that they may show gait apraxia/ataxia, shuffling gait, lymbic discoordination, bradykinesia and rigidity. Increased support time has also been found [268,269]. More recently, stride-to-stride variability has been reported to be an even more specific biomarker [270–272].

There are not many references in the literature affirming gait disturbances at the early stages of AD. Some report that these are nonexistent and gait is not useful for AD prediction [273], while others report interesting results that could be used for AD prediction. Camicioli et al. [274] affirmed that subjects developing cognitive decline walked more slowly than healthy people do, and that they presented limbic coordination impairment. Scherder et al. [268] affirmed this information and added that rigidity is already present in the first stages of the dementia. Further research is needed to verify the predictability of gait disturbances for AD.

3.4.5. Speech

The speaking and conversational skills of the AD patients deteriorate from the early stages of the disease [40]. They are likely to lose vocabulary, make big pauses while they are speaking or just stop abruptly because they are not able to continue the conversation. Thereby, speech recording aims at detecting these difficulties in speaking from the very beginning of the symptoms to facilitate an early diagnosis of AD. More specifically, their objective is to detect aphasia, which is called to the inability to communicate effectively [275]. Speech can be recorded continuously and in a non-invasive way, and can be analysed automatically with speech recognition and signal processing techniques.

Language and communication disturbances suffered by AD patients include [276] word recall and word-finding difficulties

Table 6
Behavioural features used in the literature.

Method	Reference	Features	Parameters
Smart homes	[252–255]	Sleep patterns	Sleep duration, sleep interruptions and sleep rhythms
		Outings	Number of outings, time spent out of home
		ADLs	Variation of activity patters, completion time
		Walking patterns	Number of walks, walking speed
Gait	[268,270–272]	Walking patterns	Walking speed, step length, static and dynamic postural instability, hesitation, base width, gait apraxia/ataxia, shuffling gait, lymbic disco-ordination, bradynesia, rigidity, stride-to-stride variability, support time
Speech	[27,40,286]	Hesitation and puzzlement features	Question rate, confusion rate, no answer count, rate of pauses in utterances, filler sounds
		Words	Verb, noun, pronoun, adverb, adjective, particle, and conjunction rates, unintelligible word rate
		Complexity features	Phonemes per word, words per recording, standardized word entropy, phone entropy
		Fluency	Voice segment length, pause length, short time energy and spectral centroid, voiced/unvoiced segment average, voiced/voiceless percentage and spontaneous speech evolution along the time, voiced/unvoiced segment max, min
		Emotional temperature	Pitch, standard deviation of pitch, max and min pitch, intensity, standard deviation of intensity, max and min intensity, period mean, period standard deviation, and root mean square amplitude, shimmer, local jitter, noise-to-harmonics ratio, harmonics-to-noise ratio and autocorrelation, fraction of locally unvoiced frames, degree of voice breaks
		HFD	Max, min, variance, SD

[277–280], repetitions during speech [277–279,281], loss of both reading and writing skills [280], problems to follow a conversation due to deterioration in concentration and comprehension skills [279,280] and decline in non-verbal communication skills [282]. These problems are present from the very early stages of the disease, and progress and worsen at the same time that the cognitive decline [276,283].

Due to the ease with which voice recordings can be obtained, in the recent years, speech features have been used in works related to automatic MCI and AD diagnosis systems [27,40,284–288]. Nonetheless, few studies report speech based classification results that suggest that they have potential to become part of a multimodal diagnosis system. Roark et al. have demonstrated that automatic speech characteristics measuring techniques in combination of neuropsychological tests can help in improving MCI diagnosis [287,288]. Khodabakhsh et al. [27] have recently analysed the possibility of a diagnosis, using speech features extracted from telephone calls. This is a method that could provide many advantages like, for example, to avoid displacements to hospitals or to carry out expensive tests. Using only three features, which measured the use of vocabulary and phonemes and the pause rate, 90% of accuracy was achieved by both the SVM classifier with a linear kernel and a decision tree, classifying AD patients and control people.

One of the drawbacks of speech analysis for AD recognition is that aphasias are not unique to AD, but they can be caused by other factors. Nevertheless, it is true that "AD may be one of the primary causes responsible for a high proportion of aphasic patients in the human population" [289], so it can be of great interest to continuously keep an eye on people's speech features automatically, to later verify or discard the presence of dementia. Furthermore, speech can be easily and non-invasively measured, nowadays, almost continuously, which can be a big advantage for continuous monitoring and early diagnosis systems. It remains to be seen if the accuracy reported above would be reachable in a general population, but it is clear that speech features can provide important clues for a diagnosis.

3.4.6. Others

In the review of Qassem et al. [290] some other possibilities to measure the behavioural symptoms of AD in an unobtrusive way are suggested. They propose for instance the use of motion sensors to measure restlessness, radars to measure tapping and banging behaviours, GPS tracking to detect wandering, smart beds with pressure sensing to detect sleep disturbance and video monitoring to detect shifts in ADL activities. In fact, some of these possibilities are already being researched. Examples of automatic assessment of agitation in dementia include the work of Fook et al. [291] which aim at measuring it with video streams, or the one by Bankole et al. [292] where the use of body sensors was purposed instead of cameras. In the case of wondering detection, steps have already been given so as to detect it using activity recognition techniques in wireless sensor networks [293], as said before, by means of GPS tracking systems [294] and also by using RFID tags and antennas to track the walking patterns and ADLs [295] of the patients.

3.4.7. Summary

To sum up, behavioural changes of people suffering from dementia can be assessed both by means of tests and scales carried out periodically, or automatically making use of several sensors and smart technology. Even if the tests and scales have the same inconvenients as the cognitive and psychological tests, the smart technology helps to overcome them allowing to monitor the elderly ubiquitously and in a completely transparent way. Even though it is not possible to use this technology as a definite diagnosing method, partly because it does not provide any physiological information, it is true that it could satisfactorily be used as part of a continuous monitoring system absolutely necessary for an early diagnosis. Table 6 summarizes the behavioural biomarkers of AD that have been found up to date.

4. Critical review

This section aims at critically analyzing the state of the art that has been reviewed in the previous section.

As said before, nowadays, AD diagnosis relies on cognitive assessment by means of tests such as the MMSE, on the use of CSF-based biomarkers and in the last years, on the use of some medical imaging modalities, namely, PET, CT and sMRI for brain imaging. All these methods are considered to be reliable biomarkers. However,

they present some drawbacks that make impossible their use for early AD detection.

On one hand, they only offer information about the current health condition of the patient and not about the evolution of the disorder. Data can be sampled from time to time, but may not be suitable for detecting the subtle changes which could indicate an early stage of a major problem [296] neither realistic to carry out a continuous monitoring of the disease progress [297]. Actually, they are only measured when the affected themselves or the people around them realize or suspect about the severity of the situation, and this is too late in the vast majority of the cases. Consequently, the appreciation of suffering from cognitive impairment often comes too late, when health problems already manifest themselves [298].

On the other hand, psychological or cognitive assessment questionnaires can be too subjective and may lack sensitivity [299] whereas they require the full attention of the user. Regarding CSF measurements, they are intrusive, costly and slow methods of analysis [300]. Furthermore, all of these current tests, are "usually administered in a physician's office or a rehabilitation facility, causing inconvenience for the patient, using valuable healthcare resources, making frequent monitoring unrealistic" [296] and therefore, precluding an early diagnosis. As said before (see Section 1.3), early detection of AD would bring many benefits, in terms of treatments' effectiveness and accuracy of diagnosis. There are enough evidences affirming that treatments are much more effective when they are applied in the early stages, allowing the cognitive decline to be stopped or at least, slowed down. Furthermore, when the patient is still able to answer to questions and to recall the order in where symptoms appeared, diagnosis can be much more accurate. Consequently, health-care costs can decrease while quality of life of patients can greatly improve, allowing them to make choices about their future (legal and financial decisions, how they want to be cared,. . .).

All these facts show the great importance of an early detection. Therefore, it is necessary to develop an ubiquitous monitoring system for AD and related diseases so that even the possible decisive subtle changes can be detected. Such a system should work in a completely unobtrusive and transparent manner, i.e. embedded in every day's environment, in order to be practical the massive real use. In order to achieve this goal, the two research gaps that have been identified in the literature and which are more in-depth explained in the following paragraphs should be overcome.

4.1. Multimodal analysis

Most of the recent research on AD diagnosis has been mainly focused on the search for biomarkers in physiological signals. A field much less present in the literature is that of behavioural markers. Furthermore, historically, behaviour assessment has been done by means of tests and scales whereas automatic behaviour assessment is a much more recent research subject.

This latest development has allowed to analyse behavioural features, leading to multi-domain analysis. Nonetheless, these studies use both physiological and behavioural features as independent informations, whereas the underlying relationships between the variables remain unanalysed.

Correlational studies of the literature between physiological and behavioural or psychological symptoms affirm that there exist relationships between symptoms of the different domains. Examples include the work of Tagai et al. [301], who used MRI and SPECT imaging modalities to relate anxiety of AD patients to the brain biomarkers or Poulin et al. [302] who also studied anxiety in relation to MRI markers. Delusions, apathy and agitation were also compared to markers on MRI images by others [303], as well as disinhibition and eating disorders with FDG-PET. In all of these cases, psychological and behavioural symptoms were assessed by means of tests such as the BEHAVE-AD or the NPI.

This type of studies have highly contributed in understanding the nature of AD. Nonetheless, as the emergence of ubiquitous computing and smart environments is very recent, there are not yet studies in where these both types of symptoms are related using automatic behaviour assessment methods. Therefore, such a study would be desired, not only to increase knowledge about the disorders and their effects, but also to progress towards an ubiquitous system for the early detection of these affections.

4.2. Temporal nature of AD

Current work related to AD diagnosis is mostly cross-sectional studies. The problem is posed as a classic supervised classification problem, where samples of people belonging to different groups (control, MCI and AD groups) are taken at a given time, and after applying signal processing algorithms and feature extraction techniques, part of the data is used for training purposes for the selected classifier whereas the remaining data is used for the final classification and validation purposes. This way, the validity of the signals or image modalities, the signal processing techniques, the selected features and the chosen classifiers and other parameters used in the classification model are evaluated. This process has allowed for a long time to increase our understanding and knowledge levels about the physiological process behind these disorders, as well as to move towards an earlier and more accurate detection.

AD is a disorder that progresses over time, so that its state in a certain point in time is not independent from the state in a previous point in time. Nonetheless, the vast majority of the research does not take its temporal/sequential nature into account and only a few exceptions that have used hidden Markov models have been found in the literature. Furthermore, latencies from triggers to the occurrence of symptoms are never taken into account: The correlation between multivariate signals is only analysed taking into account their values in paired moments, and not analyzing how they evolve over time. Longitudinal studies allow to see these changes over the course of time, both to analyse how the situation under investigation affects an individual or to see the group differences that can be found over time, as well as to clarify the sequences in variables and deduce correlations and causalities.

Therefore, it is necessary to focus more on methods that exploit the behaviour of symptoms longitudinally, treating them as temporal or sequential signals and applying the correspondent analysis techniques, which could help discover heretofore unknown patterns.

5. Useful tools for AD research

The scientific community is turning increasingly to research on Alzheimer's and this is partly due to the availability of data and tools for this purpose. In this section, we briefly review the existing public AD databases, in addition to the so necessary image processing basics and the neuroimaging processing toolboxes which are available to researchers.

5.1. Publicly available AD datasets

In the recent years, several longitudinal studies have been carried out and the resulting datasets have been made available to the scientific community in order to facilitate the research of MCI and AD biomarkers that could lead to an earlier detection of the disease.

- Physiological data

  Regarding physiological data, one of the best known publicly available databases is ADNI [99]. It is a big multi-site project and

it has been funded by the US National Institutes of Health in a partnership with the pharmaceutical industry [304]. The initiative was launched in 2003 and it's currently on its third phase (ADNI, ADNI GO and ADNI 2). ADNI's main goal has been to analyse the progression of MCI and early AD by means of clinical and neuropsychological tests, MRI and PET brain imaging modalities and some other biological markers, so as to identify sensitive and specific biomarkers for early AD detection [28]. Some remarkable works have resulted from this database, allowing to increase our understanding about the disease. For example, thanks to ADNI, it is currently known that AD starts to develop many years before symptoms are manifested [305,306], as well as the order in which biomarkers become abnormal [307,308] or the order in which atrophy of the brain occurs [309,310]. Identification of new biomarkers (in blood [311], α-Synuclein [312],. . .) is also in progress. The review of Weiner et al. [313] highlights the major findings of the ADNI database up to 2015. Besides, ADNI has also encouraged the creation of other datasets of similar characteristics [313].

Another MRI dataset available thanks to the Washington University AD Research Center, Dr. Randy Buckner at the Howard Hughes Medical Institute at Harvard University, the Neuroinformatics Research Group at Washington University School of Medicine, and the Biomedical Informatics Research Network (BIRN) is the Open Access Series of Imaging Studies [314]. It contains both longitudinal and cross-sectional datasets where people of different cognitive states are included, starting from healthy subjects to elderly with mild to moderate AD.

The Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing [315] is a longitudinal study database and it is active since November 2006. It includes MRI and PET imaging data of healthy subjects, and MCI and AD diagnosed subjects, as well as their medical history, neuropsychological scores, blood analysis and other non-imaging data.

The Minimal Interval Resonance Imaging in AD database is also publicly available on the web [316] since 2013. This dataset includes MRI scans of both AD diagnosed people and healthy-subjects taken at different time intervals. The aim of the study was to investigate the usefulness of MRI for clinical trials of AD treatments.

The National Alzheimer's Coordinating Center [317] also offers a database with clinical evaluations, neuropathology data and MRI imaging of people with AD or related disorders, with MCI and healthy subjects.

- Behavioural data

  Although in a much smaller amount, there are also some behavioural datasets available for researchers. For example, the Oregon Center for Aging and Technology [318] has made accessible a database where longitudinal in-home activity sensor data of some elder is included, as well as their health forms and neuropsychological tests. Data of the Dem@care project [319] is also available under request, where audiovisual recordings and sleep, motion and physiological data collected in the Greek Alzheimer's Association for Dementia and Related Disorders and in participants' homes can be found.
- Others

  Genomics Databases such as The National Institute on Aging Genetics of AD Data Storage Site [320] also exist.

5.2. Standard methods for medical imaging analysis

The use of the aforementioned brain imaging modalities for AD research, involves having to apply several image processing techniques, which will be selected depending on the nature of the images to be treated and their specific characteristics. The common steps for medical image analysis are listed below [321]:

- Enhancement

  The aim of enhancement algorithms is to reduce image noise, to increase the contrast of structures of interest and to improve the spatial resolution. They enhance the quality of the image, and might ease the subsequent diagnosis both visually or by means of (Computer Aided Diagnosis) CAD systems. Linear, non-linear, fixed, adaptive, pixel-based or multi-scale methods exist for this purpose. Basic image enhancement techniques are thoroughly explained in [322].
- Segmentation

  Segmentation is the process of dividing an image into regions with similar properties [323], therefore, to subdivide the objects in an image [324]. It allows to study the anatomical structure, to identify ROIs, to measure tissue volumes, and so on. This group of algorithms includes techniques like thresholding, region growing, deformable templates, edge-based segmentation and pattern recognition techniques such as neural networks and fuzzy clustering. Measurements and following processing steps rely on segmented regions, so it is a crucial step. [325]
- Quantification

  Once the images have been segmented, quantification algorithms can be applied so as to obtain diagnostic information such as the shape, size, texture, and density of tissues, musculoskeletal angle, kinematics, and stress or ventricular motion, myocardial strain, and blood flow [326]. The aim of quantification is to obtain precise, fast, repeatable and objective measurements of these properties. Refs. [327,328] explain the basics of 2-dimensional and 3-dimensional quantitative analysis, respectively.
- Registration

  The aim of image registration is to "determine a spatial transformation that will bring homologous points in images being registered into correspondence" [329]. Registration of images is usually required to enable comparisons between both cross-sectionally and longitudinally obtained images. The algorithms used for this purpose should overcome distortion problems caused by differences in imaging methods, their artifacts, soft tissue elasticity and variability among subjects. Specially, PET [330] and MRI [331] modalities are affected by this type of distortions, due to hardware imperfections, motion of subjects and to the intrinsic physics behind the image acquisition and reconstruction process. A throughout review of medical image registration techniques was recently published by Oliveira and Tavares [332].
- Visualization

  Graphics hardware and software specifically designed to facilitate visual inspection of medical data should be mentioned herein. Objectives of visualization algorithms are to generate realistic displays for presentation of images and other information in three or more dimensions, to develop interactive and automated methods for manipulation of images and other data, to implement measurement tools for quantitative evaluation and to design and validate models that ease the interpretation and decision-making process from the images [333,334].
- Compression, storage and communication

  Storage of medical images should be done in an efficient manner so as to facilitate their sharing, and this implies the use of compression algorithms, specialized formats and standards. Compression of images requires to adopt a trade-off between the storage size and information loss. Examples of compression standards include JPEG, MPEG, and Wavelet and Fractal Compression, while standards like DICOM and HL-7 are defined for communication and storage purposes. The use of these standards is recommended to ensure interoperability. For further information, the reader can refer to [335,336].

5.3. Neuroimaging processing toolboxes

Although some years ago neuroimaging analysis was done by visual inspection, currently, there exist methods that allow to carry out an objective (quantitative) analysis. The automated analysis of brain images requires good image processing skills, as well as a sound knowledge about brain anatomy. In order to ease this process, researchers can take advantage of the variety of freely available toolboxes.

The statistical parametric mapping (SPM) [337] is a toolbox for the voxel-based morphometry (VBM) analysis of the brain from fMRI, PET, SPECT, EEG and MEG data sequences. It entails a voxel-wise comparison of local brain volumes and it performs spatial normalization, segmentation, modulation, and smoothing [338]. It is probably the most commonly used software for brain imaging analysis in AD research. The first release was published in 1991 and the current version is the SPM12 and during all these years it has highly contributed to AD research [110,338,339].

Extensions to SPM are also available, for example, the "computational anatomy toolbox" [340], which allows to apply diverse morphometric methods such as VBM, surface-based morphometry, deformation-based morphometry (DBM), and region-based or label-based morphometry. Another example is the "individual brain atlases using statistical parametric mapping software" [341], which is an MRI segmentation tool based on MATLAB and SPM. It allows to automatically segment brain structures and to compute the volume of gross anatomical structures.

FreeSurfer [342] is an open source tool for processing and analyzing MRI images, but it also allows to work with fMRI data. Among its features are segmentation, cortical thickness estimation, surface reconstruction, both cross-sectional and longitudinal data processing, etc. In contrast to the VBM which is based on volumetric techniques, FreeSurfer uses geometry to perform inter-subject registration.

SurfStat [343], is a Matlab-based toolbox for the statistical analysis of univariate and multivariate surface and volumetric data for VBM, DBM and PET data. It enables to deal with repeated-measure data by applying mixed-effects and random-field modeling.

The "extensible Matlab medical image analysis" [344] toolbox allows to perform this kind of image processing in Matlab, while "data processing assistant for resting-state fMRI" [345] enables the application of several popular analyses on MINC files. Besides, FMRIB Software Library [346] is an independent library that allows to analyse fMRI, MRI and DTI data.

Other tools [347–349] are also available, and the selection of one or the other depends on the images to be processed, the characteristics or features to be generated and the requirements and dependencies of each tool. An extended list of free software solutions for neuroimaging and medical imaging analysis can be found in the "neuroimaging informatics tools and resources clearinghouse" website [350].

6. Real-world datasets' issues

Currently existing datasets for AD research, such as the ones mentioned in Section 5.1, contain huge amounts of data. Data Mining and Machine Learning algorithms are being applied to these data in order to find out new biomarkers that could lead to an earlier detection of the disease. It is generally accepted that better results can be achieved, if quality of the dataset is ensured.

Quality of the data will be considered satisfactory when some conditions are fulfilled [351]. In this section, two common issues related to the use of multimodal and multi-site real world datasets which might jeopardize the quality of the datasets and therefore, of the results, are discussed.

6.1. Mislabeled data

Supervised learning algorithms rely on the labels of the training data to learn the underlying relationships and patterns that may exist. Hence, incorrectly labeled data might deteriorate the system performance due to the presence of noise and increase its complexity since non-real patterns may also be modeled [352]. This incorrectly assigned labels are known as "class noise", "misclassifications" or "mislabeling". Some authors also consider to be class noise the data outliers that might be correctly labeled but are quite rare instances. Of course, attributes' or features' noise can also affect the results of learning algorithms, but the greater importance that the class labels have on this issue has been demonstrated both in [353,354].

Class noise itself can be distinguished into two different problems: contradictory examples and mislabeled examples. While the former happens when different labels are assigned to the same attributes' values, the latter concerns the case when the instances are assigned to a different class than the real one.

Mislabeling is a typical problem in real-world datasets and may be caused by several issues [355]. For instance, data might be incorrectly labeled due to human errors. When an expert physician is asked to label a big dataset, he might easily get confused due to time pressure, due to not paying enough attention to each individual case, etc. When labeling is done by machines, design faults or too similar cases can lead them to incorrectly label the data. Classes can also be wrongly introduced when datasets are being digitalized, or might be lost or incorrectly copied if manipulation and backing up is not done carefully. Furthermore, in the multi-domain and multi-modal approach being proposed herein, sources of contradictory labeling multiply. The unified analysis of data coming from very different sources, requires dealing with labeling done by different experts, scores resulting from different cognitive assessment tests or evaluation done by any other different criteria. Therefore, the multi-modal and multi-domain analysis leads to an even higher ambiguity.

As said in Section 1, the only 100% reliable AD diagnosis is achieved by a post-mortem analysis of the brain, which is normally no an option when collecting data for publicly available datasets. Therefore, there is a risk that existing datasets are incorrectly labeled, and this is an important issue for practical machine learning [356,357]. These datasets are commonly accompanied by an MMSE score, but other assessment scores are also used, for example Clinical Dementia Rating or GDS. Sometimes, more than one of these scales are assigned to the same data, which can provoke an ambiguous labeling. Or it might also happen that data of different modalities of the same subject is labeled following a different criterion or different experts' opinion: for example, AD severity might be evaluated using MR images by an expert physician, and a different cognitive score might be given by another expert when evaluating PET images of the same subject.

Even if handling the data cautiously, taking the necessary time to analyse each instance of the data and defining clear and unified criteria to label the data might help, it is assumed that class noise will always exist in a greater or lesser extent. So as to overcome this problem, several approaches have been developed in the recent years [357]. Some of them aim at filtering the misclassified data before applying the classification algorithms [352,358–360], while others aim at performing a robust classification despite the class noise (the so called "noise-tolerant" techniques) [361–363]. This type of approaches have been applied in the medical diagnostics' domain with satisfactory results [355,351,364].

Therefore, it is of great importance to be aware of the problem that class noise poses to all classification problems which deal with real-data, but specially to the medical domain, where peoples' health and life are at risk. It is necessary to take the sufficient time to

analyse the ambiguities of the data and to apply class noise filtering algorithms or noise-tolerant classifiers. Hopefully, a standard to assess cognitive impairment levels with a high reliability will be available within few years so that the problem of class noise can be reduced.

6.2. Multi-site neuroimaging data

In order to achieve an improved statistical power in investigating neuroanatomic correlates of AD, it is necessary to collect the larger number of samples possible. The most practical solution for this purpose is to obtain data from different patient populations and pool the collected data across multiple sites [365]. Furthermore, this type of datasets increase the options to acquire geographically distributed data, to have a wider variety of patient types, etiologies, and range of symptoms, being better representatives of the population under study.

Nevertheless, a big challenge exists in pooled datasets and studies: technology-related variability in the images must be minimized [366] because it might limit the power to model AD progression and to find reliable biomarkers. Data interpretation might be affected due to variation across centres, even if the same scanner model is being used, as they might slightly differ, for example in MRI scanners, in field inhomogeneity effects [367].

In order to control this type of variance, standardized phantom studies should be used and strict quality imaging protocols must be assured [368]. The Morphometry BIRN [369] Testbed is one of the projects that aims at developing methods for data collection, combination and sharing from imaging protocols. They have analysed the feasibility of pooled analyses of MRI data in normal aging and AD, using rigorous data curation, image analysis and statistical modeling methods on data of three different sites. They have concluded that MR data from multiple sites can be satisfactorily pooled to investigate questions of scientific interest. Furthermore, they found out that the use of methods such as mixed-effects models considering site as a random effect, allows to take advantage of expected comparability of age-related effects while accounting for site specific effects.

Despite this major challenge, the number of multi-site clinical trials has dramatically increased in the last years [370]. This is an indicator of the recognition that policy makers and funding organizations give them, and a sign that they understand that all the scientific, clinical and financial investment on these type of datasets is worthy. ADNI [99] is an example of a successful multi-site database in the case of AD, but other similar databases for other diseases also exist, for instance, the Collaborative Initiative on Fetal Alcohol Spectrum Disorders [371] or The Pediatric Brain Tumor Consortium [372].

7. Conclusions

AD is a disorder that affects millions of people in the world, and this number will continue increasing according to all prospects. Other than it is a serious problem that still today there is no cure for this disease, it is of even much more concern the lack of reliability and the tardiness in the diagnosis. Two main problems have been spotted: on one hand, patients and their family members and friends do not realize about AD symptoms until being too late, so when they attend specialists the treatments for delaying the symptoms are not already effective. On the other hand, specialists have real difficulties for diagnosing AD, because not all physiological changes can be easily detected and furthermore, most of the biomarkers are not unique to AD. A solution capable of dealing with these problems is needed in order to achieve early AD diagnosis that could improve the life quality of the patients and of the people close to them, reducing the effects of the disease and increasing their life expectancy.

Due to the fact that most of AD symptoms are not unique to AD, it is necessary to find a unique combination of biomarkers for this disease, which could allow to make a reliable diagnosis, at the most earliest stage as possible. This combination will not be found using signals or images of a single type: a multimodal system must be implemented in order to take full advantage of all kinds of symptoms, detect even the smallest changes and combine them, so as to detect AD as early as possible.

This system, must be able to continuously monitor the elderly at risk of AD, so as to detect symptoms that the patients themselves and the people nearby miss. Therefore, an ubiquitous and transparent monitoring system is desired.

The multimodal symptomatology, as well as systems for monitoring and detecting them have been reviewed in this article. A summary of the reviewed literature can be found in Table 7. It has been seen that cognitive and psychological symptoms can currently only be measured by means of tests or questionnaires, and therefore, cannot be integrated in an automated continuous monitoring environment. Consequently, such a system must be based on physiological and behavioural symptoms' measurements. While behavioural changes can be monitored ubiquitously, and in a completely unobtrusive and transparent way for the user, being an essential part of an early diagnosis methodology, physiological changes must be mandatorily monitored and identified for the diagnosis to be reliably done.

Some physiological signals and images seem to be more adapted for this purpose than others. The reviewed results suggest that MRI is among the most powerful tools for detecting AD, but other methods such as the use of EEG, DTI and eye dynamics seem to be promising for the earliest signs. Furthermore, they are not invasive methods as could be PET or SPECT imaging techniques or blood and CSF tests.

Regarding the behavioural monitoring, smart homes provide a powerful tool that can be easily integrated in the real life of the elderly, automatically detecting the behavioural symptoms from the very beginning, without obstructing their daily activities. Likewise, gait anomalies, wandering and other symptoms can also be detected through the use of wearables or smartphones.

In the critical analysis of the state of the art, two gaps have been identified: on one hand, the lack of multimodal systems for AD detection, and on the other hand, the absence of ubiquitous systems that monitor patients continuously and analyse their temporal data.

Tools that might help in the development of a system of these characteristics exist. In this line, both physiological and behavioural datasets of AD patients are available to the research community. The processing and analysis of biomedical images involve consideration of some standard steps that have been reviewed herein. Moreover, even if the analysis of neurological images might suppose a trouble for researchers who are not experts in image processing and neuroanatomy, toolboxes to ease this process exist and are freely available. Nonetheless, some basic skills about these subjects remain necessary for their proper use.

Some issues might appear when working with multimodal datasets, as proposed in this paper. On one hand, datasets are labeled using different criteria, and therefore, their combination might not be trivial. Furthermore, this criteria has rarely been the result of the post-mortem diagnosis of AD patients, which may imply some data to be incorrectly labeled. Methods to overcome this "noisy labeling" exist: both filtering methods to detect and remove these erroneous data and machine learning algorithms that get over this drawback. Therefore, it is important to take into account the possible presence of noisy data when working with our datasets and to apply the appropriate method for each case. Mixing

Table 7
Reviewed literature.

Reference	Dataset	Subj.	Signal	Feature red.	Classification	Best results
[113]	OASIS	90	MRI	–	ANN	CTL vs AD: 83%
[26]	ADNI	218	MRI	–	SVM + Bayes + SVM	CTL vs AD: 87, MCI vs AD: 72.23, MCI vs CTL: 78.22
[28]	ADNI	818	MRI	Thresholding (intensity > 10% max. intensity)	SVM	AD vs CTL: 88.49, AD vs MCI: 78.92, MCI vs CTL: 85.4
[373]	ADNI	800	MRI	–	SVM	AD vs CTL: 85.7, MCI vs CTL: 78.2
[56]	ADNI	834	MRI	–	LDA &SVM	AD vs CTL: 89, pMCI VS CTL: 84, pMCI vs sMCI 68
[112]	OASIS	457	MRI	–	ANN	89.22
[30]	ICBM + Centro San Giovanni	299	MRI	–	SVM, LDA, QDA	82 (SVM)
[105]	ADNI	829	MRI	PCA, k-best	SVM	AD vs CTL: 98.95, AD vs MCI: 87.3, MCI VS CTL: 90.64
[114]	ADNI	60	MRI (long.)	DA	SVM (RBF)	AD vs CTL: 91.7
[115]	ADNI	132	MRI (Long.)	Lasso regularization	Logistic regression (LR)	MCI vs AD: 60 in males, 83.78 in females
[134]	ADNI	40	fMRI	–	SVM	97.5
[135]	Washington Univ. ADRC	41	fMRI + MRI	Symmetrical uncertainty (correlation)	Improved RF	AD vs CTL: 88, AD1 vs AD2 vs CTL: 80.5, AD1 vs AD2 vs CTL1 vs CTL2: 87 (only fMRI)
[136]	–	41	fMRI	Symmetrical uncertainty (correlation)	RF	AD vs CTL: 95.5, AD1 vs AD2 vs CTL: 87, AD1 vs AD2 vs CTL1 vs CTL2: 93
[19]	–	73	DTI	ReliefF algorithm	SVM (RBF)	MCI vs CTL: 92.9, MCIna vs MCIa vs CTL:92.785
[173]	Duke-UNC BIAC	27	DTI + fMRI	–	SVM (mixed kernel)	MCI vs CTL: 96.3
[174]	–	137	DTI + MRI	Information gain (IG) criterion	SVM (RBF)	AD vs CTL: 80.3 FA, 83.3 MD, 82.7 WMD, 89.3 GMD
[82]	ADNI	375	18F-FDG-PET	–	SVM (linear &RBF)	AD vs CTL: 94.6 (LDA, linear SVM), AD vs MCI: 81 (PCA, RBF), MCI vs CTL: 79.7 (LDA, RBF)
[83]	ADNI	57	11C-PiB-PET &18F-FDG-PET	PCA	SVM (multi-kernel)	CTL vs AD: 94.12, CTL vs MCI: 82.05
[84]	ADNI	219 + 91	PET &SPECT	–	SVM linear &quadratic	96.7 AD vs CTL quadratic &SPECT
[86]	–	60 + 79	PET &SPECT	–	Bayes	98.3 PET, 88.6 SPECT
[85]	ADNI	401	PET	–	SVM	AD + MCI vs CTL: 77.97, AD vs CTL: 88.24, MCI vs CTL: 70.21
[97]	Virgen de las Nieves Hospital	52	SPECT 99mTcECD	FDR	SVM (RBF)	90.38
[98]	Virgen de las Nieves Hospital	79	SPECT 99mTcECD	–	SVM (RBF)	96.91
[94]	Virgen de las Nieves Hospital	79	SPECT 99mTcECD	*t*-test with feature correlation weighting	SVM (linear)	98.3
[196]	–	286	EEG	ANOVA	IFAST (ANN)	CTL vs MCI: 93.16
[198]	Rome's Neurology Unit of Policlinico Campus Bio-Medico	272	EEG	MS-ROM	kNN, naïve Bayes, QDC	AD vs CTL: 93.48, AD vs MCI: 94.05, CTL vs MCI: 97.88
[197]	–	295	EEG	IFAST noise elimination	IFAST (ANN)	AD vs MCI: 92.33
[195]	–	143	EEG	IFAST	IFAST (ANN)	MCI vs MCI/AD: 85.98
[199]	–	35	EEG	–	SVM (RBF)	AD vs CTL: 79.9, AD vs CTL (personal): 86.97
[35]	–		EEG	Manual	SVM (quadratic)	MCI vs CTL: 96.8, AD vs CTL: 96.9, AD vs MCI: 90.9, AD vs MCI vs CTL: 85.4
[211]	–	41	MEG	–	ANFIS (fuzzy)	AD vs CTL: 85.37
[212]	–	62	MEG	–		77.42 (SSE)
[213]	–	41	MEG	–		87.8
[214]	–	24	MEG	–		70.83
[284]	–		Speech	–		
[27]	–	40	Speech	–	SVM, LDA, DT	90 (SVM &DT)
[286]	–	40	Speech	–	MLP	93.02
[40]	–	40	Speech	–	SVM	97.7
[221]	–		Eye movement	–	SVM (RBF), Bayes, LR	87 MCI vs CTL SVM
[229]	–	25	Eye movement	–		
[255]	ORCATECH	97	Smart homes	Remove-one-feature process	SVM	AUC of the ROC curve of 0.97 and AUC of the precision-recall curve of 0.93
[256]	CASAS	18	Smart homes	–	SVM	cognitively best vs worst: 71.75
[113]	OASIS	98	MRI	–	ANN	83
[252]	–	14	Smart homes	–	–	–
[254]	–	14	Smart homes	–	–	–
[253]	–	109	IADLs	–	–	–
[270]	–	16	Gait	–	–	–
[271]	–	427	Gait	–	–	–
[272]	–	57	Gait	–	–	–

data of different sites might also pose a problem due to differences in hardware or imaging protocols, but as it has been seen shown in this paper, standardized phantom studies, rigorous data processing and statistical modeling can successfully help in overcoming this issue.

An unobtrusive and transparent early AD diagnosing method is yet to be developed. This article has reviewed the state of the art in AD diagnosis, emphasizing in automatic and CAD systems, in order to facilitate and accelerate the design and development of such a system that can overcome the current biggest challenge of AD.

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