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Review

# Early diagnosis of Alzheimer's disease: the role of biomarkers including advanced EEG signal analysis. Report from the IFCN-sponsored panel of experts

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HIGHLIGHTS

- This review describes an integrated and multidisciplinary approach for the "early" diagnosis of Alzheimer's disease (AD).
- An overview of epidemiology, genetic risk factors, and different biomarkers of AD is provided.
- Latest findings suggest EEG rhythms analysis as a valid screening tool to predict AD conversion.

ABSTRACT

Alzheimer's disease (AD) is the most common neurodegenerative disease among the elderly with a progressive decline in cognitive function significantly affecting quality of life. Both the prevalence and emotional and financial burdens of AD on patients, their families, and society are predicted to grow significantly in the near future, due to a prolongation of the lifespan. Several lines of evidence suggest that modifications of risk-enhancing life styles and initiation of pharmacological and non-pharmacological treatments in the early stage of disease, although not able to modify its course, helps to maintain personal autonomy in daily activities and significantly reduces the total costs of disease management. Moreover, many clinical trials with potentially disease-modifying drugs are devoted to *prodromal* stages of AD. Thus, the identification of markers of conversion from *prodromal* form to clinically AD

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may be crucial for developing strategies of early interventions. The current available markers, including volumetric magnetic resonance imaging (MRI), positron emission tomography (PET), and cerebral spinal fluid (CSF) analysis are expensive, poorly available in community health facilities, and relatively invasive. Taking into account its low cost, widespread availability and non-invasiveness, electroencephalography (EEG) would represent a candidate for tracking the prodromal phases of cognitive decline in routine clinical settings eventually in combination with other markers. In this scenario, the present paper provides an overview of epidemiology, genetic risk factors, neuropsychological, fluid and neuroimaging biomarkers in AD and describes the potential role of EEG in AD investigation, trying in particular to point out whether advanced analysis of EEG rhythms exploring brain function has sufficient specificity/sensitivity/accuracy for the early diagnosis of AD.



**Contents**



## 1. Introduction

Alzheimer's disease (AD) is characterized by a progressive loss of memory and deterioration of other cognitive functions. The typical AD clinical phenotype follows a prodromal stage known as Mild Cognitive Impairment (MCI): although quite heterogeneous, it is usually characterized by memory loss (amnestic MCI, aMCI) and represents a transitional state between normal aging and AD. Annually, 10–15% of patients diagnosed with MCI progress to AD dementia (usually *MCI prodromal-to-AD*), at a considerably accelerated rate compared with healthy age-matched individuals, estimate around 1–2% (Petersen et al., 1999; Tierney, 2001). The identification of reliable markers able to intercept those MCI who are in a prodromal stage may allow for developing early interventions. In fact, even in the absence of a disease-modifying therapy, several lines of evidence suggest that starting pharmacological and non-pharmacological treatments (including changes in lifestyle) in the early and/or prodromal stage of disease helps maintain personal autonomy in daily activities and significantly reduces the total costs of disease management (D'Amelio and Rossini, 2012; Teipel et al., 2015; Petersen et al., 2017). Moreover, *MCI prodromal-to-AD* subjects are the main targets of many of the ongoing clinical trials with potentially disease-modifying drugs (DMDs), since these drugs have proved ineffective when full symptomatology of AD has been already developed. Therefore, early markers predicting with high sensitivity/specificity the evolution from prodromal stages to clinically overt AD are of pivotal importance. Although this goal can be partly reached with the presently available diagnostic armamentarium – volumetric magnetic resonance imaging (MRI), positron emission tomography (PET), PET + radioligands, lumbar puncture for amyloid and tau metabolites –, all of these markers have a relatively low sensitivity to synaptic dysfunction (the very early stage of pre-symptomatic AD). Moreover, most of them are expensive, poorly available on community health facilities and relatively invasive. Taking into account its low cost, widespread availability and non-invasiveness, electroencephalographic signals (EEG) analysis may be an excellent candidate for tracking the prodromal phases of cognitive decline in routine clinical settings. This review paper was prepared under the endorsement of the International Federation of Clinical Neurophysiology (IFCN) and is the result of an "Experts Workshop" held in Rome in June 2017. The first part of this paper provides an overview of the epidemiology and genetic risk factors as well as of neuropsychological and neuroimaging biomarkers in AD. The second part summarizes the key issues and the most recent findings about the application of EEG in AD evaluation,

pointing out whether advanced analysis of EEG rhythms exploring brain function has sufficient specificity/sensitivity/accuracy for the early diagnosis of AD as a first level approach forscreening out the risk of conversion from MCI to AD.

## 2. Epidemiology of AD and dementias

The AD phenotypes and syndromes classification has improved substantially over the last decade. The diagnosis in the preclinical phase is based largely on limited and selected data from few tertiary centers. There are few and limited population-based data on the issues of new classification systems and diagnosis anticipation. Population-based data with the use of new, including advanced markers, and old criteria originate from the Mayo Clinic Study on Aging (MCAS) as part of the study of the Rochester Epidemiologic Project (Rocca et al., 2018).

In everyday clinical activity, the prompt diagnosis of dementia is missed in a large number of cases using the old NINCDS-ADRDA criteria (Rait et al., 2010). This is evident comparing data from the active search in population-based studies as CFAS (Cognitive Function and Ageing Studies) and EURODEM with data from files of the GPs of the national UK database (passive ascertainment based on referral). The misdiagnosis or missed diagnosis is much larger in the >80 age groups compared with lower age groups. This is relevant considering that two out of three patients with AD will be over age 85 by 2050. One of the most interesting questions is the time trend of dementia incidence. Dementia prevalence is steadily growing, caused both by the aging and increased life expectation of the general population. This is a worldwide phenomenon, but China, India, Indonesia and Brazil drive these demographic changes as a result of the huge size of their population. Recent prevalence data from CFAS in the elderly population (older than 65) from six geographic areas in England and Wales show that dementia prevalence estimated in the period 2008–11 was almost 25% less than what was predicted based on prevalence data estimated in the period 1989–94, in the same area (Matthews et al., 2013). Consistently, CAFS report a drop in incidence of about 20%, mainly determined by a decline in incidence among males (Matthews et al., 2016).

Similarly, in the Framingham Study a population-based investigation (Satizabal et al., 2016) has been conducted looking at dementia incidence time trends in five thousands elderly (more than 60) within the period 1977–2008, divided in four 5-year intervals. The cumulative dementia incidence rates declined from 3.6/100 to 2.0 per/100 person year. Dementia declined about 44% in the more recent period only in subjects with at least high school diploma, and the decline was both for AD and vascular dementia. In the same period, there was an increase in diabetes, obesity and hypertension. On the other side, there was an increase in number of hypertensive subjects with medical treatment, a reduction of stroke, a decrease in the prevalence of smoking, an increase of average levels of high-density lipoprotein (HDL) cholesterol. Furthermore, there was really a dramatic increase in education, with subjects holding a college degree going from 13 to 34%. Several causes and possible interactions of these changes have still to be identified.

All these data show that – under appropriate lifestyle modifications – dementia incidence is declining in a relatively short period of time, similarly to what happened previously for myocardial infarction and stroke (Mozaffarian et al., 2015). These changes indicate that dementia is largely preventable. In the last two decades, several observational studies have shown a wide variety of potentially modifiable risk factors for cognitive impairment and dementia (Livingston et al., 2017), which have been proposed as targets for preventive strategies. In addition to cardiovascular risk factors, psychological conditions, education level, engagement in social and mentally stimulating activities, sensory changes, and lifestyle including diet, physical activity and voluptuary habits have obtained a crucial role (Livingston et al., 2017). The recognition of modifiable risk factors and successive intervention may be part of a population strategy that could lead to a significant decrease of about 30% of dementia cases, according to conservative estimates recently published (Norton et al., 2014).

## 3. Cost effectiveness of early diagnosis in AD

AD was estimated in 2010 to cost about $604 billion in United States (US) annually. These costs are staggering, particularly taking into account the predictions for the growth in the worldwide number of AD cases (Wimo et al., 2013), that will increase rapidly in the next decades. In the US, the global costs of dementia were estimated to be $818 billion in 2015, with an increase of 35% since 2010; 86% of the expenses are incurred in high-income countries. The costs of informal care and the direct costs of social care still contribute within similar proportions to the total cost, whereas the cost of the medical sector is much lower. The threshold of US $1 trillion is currently being crossed (Wimo et al., 2017). The advantage for an early diagnosis of AD in a scenario that does not permit disease- modifying therapy (DMT) is still debated and, in absence of such therapies, programs devoted to screen general old population for AD could appear useless. On support for an early diagnosis of AD, it is generally thought that also the treatment with Choline Esterase inhibitors (ChEi) is more effective when used before widespread pathological changes have occurred (Cummings et al., 2008; Hogan et al., 2008).

On this field, several neuro-economic investigations have provided reliable recommendation about the effect of an early diagnosis on the social cost and the advantage in patient management. In particular, timely detection and symptomatic intervention in AD can be cost-effective because even though having limited efficacy, they nonetheless control symptoms enough to reduce healthcare costs and keep patients living longer in the community (Geldmacher, 2008). Moreover, a UK study based on 2007 costs estimated that in ten years timely detection and treatment produced savings of £3600 (US $5508) in direct costs and an additional amount of £4150 ($6350) in indirect costs (caregiver time) per patient (Getsios et al., 2012).

Despite the burden posed on individuals and the health care system, diagnosis of AD is clearly suboptimal. For instance, the UK National Audit Office estimates that more than half of all cases of AD in the United Kingdom are undiagnosed.

Recently, Barnett and coworkers (2014) explored the effect of an early diagnosis and interventions in the Paquid cohort. They calculated the economic effects of moving AD diagnosis from the real standard diagnosis – Mini-Mental State Examination (MMSE) 18 – to the previous 8 years. They applied a statistical model in which a symptomatic treatment that improve cognition by one MMSE point would produce a maximum net cost benefit when applied at the earliest time point and this effect would drop 17% for each year of delayed diagnosis. In contrast, for a scenario where a DMT halting cognitive decline for one year, economic benefits would peak when treatment effects were applied two years prior to standard diagnosis. In this case, the effect would be fifteen times greater than in the symptomatic one. It is clear that the modification of the clinical trajectories with both symptomatic drugs and DMT could have enormous consequences on the general cost of AD management. This offers a challenge for all Health Services, which should be prepared to face an increasing number of subjects with dementia. Besides, when we pass to the scenario of DMT availability, the diagnosis will move from AD to *prodromal-to-AD*

states. In such condition, clinical criteria are unlikely to be appropriate and progressively investigations that are more expensive will be required.

## 4. Overwiew on AD markers

According to recent indication of the National Institute on Aging and Alzheimer's Association (NIA-AA) Research Framework, AD is defined by its underlying pathologic processes that can be documented by postmortem examination or in vivo by biomarkers, shifting the definition of AD in living people from a syndromic to a biological construct (Jack et al., 2018). Therefore, when looking at AD as a continuum, the role of the markers is essential to track the evolution of disease and especially to allow an early diagnosis starting from pauci- or asymptomatic disease stages. The concept of *MCI prodromal-to-AD* has been introduced from a panel of international experts (Dubois et al., 2010, 2014). They showed that if neuropsychological tests are combined with information from neuroimaging (both structural and flow/metabolic), cerebral spinal fluid (CSF) analysis and genetic risk evaluation, one can predict with high accuracy the evolution to AD in MCI subjects at an individual basis or – better – MCI subjects who are already in a stage *prodromal-to-AD* can be promptly intercepted. Subjects with a prodromal stage of AD (IWG-2 – International working group – criteria, Dubois et al., 2014) or *MCI prodromal-to-AD* (NIA-AA criteria, McKhann et al., 2011) are the main targets for the employment of diagnostic/prognostic markers. MCI can be defined *"as an intermediate clinical and neuropsychological state between normal cognition and AD dementia, mainly characterized by objective evidence of memory impairment during a neuropsychological examination that does not yet encompass the definition of AD dementia"* (Vecchio et al., 2018). Epidemiological research suggests that aMCI is a precursor of AD, based on the high rate of progression from this state to AD. Not all MCI subjects convert to dementia, either remaining in the MCI condition or returning to a fully normal one, but many, between 50 and 60%, do it.. In order to promote early prompt therapeutic and organizational strategies, the diagnosis of the MCI condition and the prognosis on the likelihood and time of progression to dementia should be should be achieved simultaneously. The MCI definition requires the following: cognitive questionnaire, screening tests (MMSE), neuropsychological evaluation – including 2 tests for episodic memory, tests for language, visuo-spatial abilities and behavioral scales with appropriate normative thresholds (Cerami et al., 2017; Costa et al., 2017) –, functional scales, neurological examination and a CDR (Clinical Dementia Rating) score of 0.5. Growing evidence suggest that early diagnosis reduces health and social costs for dementia management. Moreover, *MCI prodromal-to-AD* is becoming progressively more frequent and is the preferred target for clinical trials with potential DMDs. To date, several tests combined together (i.e. hippocampal volumetric MRI, $^{18}$F-FDG PET and lumbar puncture for CSF examination) allow diagnosing early *MCI prodromal-to-AD* with a high degree of sensitivity and specificity. Because of their elevated costs, low availability and/or invasiveness, these cannot be applied to evaluate a large population sample on a nationwide scale. In a recent study by an international consortium (Cohort Studies Memory in an International Consortium-COSMIC - Sachdev et al., 2015) it was attempted to define the epidemiological boundaries of the MCI condition by a metanalysis of the published data. A prevalence of 5.9% has been estimated in a population with >60 year, with an increment of the stratified age ranges from 4.5% (60–69 years), to 5.8% (70–79 years) and 7.1% (80–89 years). On this basis, – even if this scenario is not accepted by all the Experts (see Petersen et al., 2018) – just for example, for the 2016 in European Community population an estimated number of about 8.000.000 MCI subjects can be predicted.

### 4.1. Genetic markers

Three decades of genetic research have substantially broadened our knowledge about pathogenic mechanisms leading to neurodegeneration and dementia, starting, however, from very rare forms of AD. In the 20th century, genetic linkage analysis identified three major causes underlying genetically dominant early onset forms of AD (ADAD) such as amyloid precursor protein (*APP*), and Presenilins (*PSEN1* and *PSEN2*) genes (Goate et al., 1991; Levy-Lahad et al., 1995; Sherrington et al., 1995). Mutations of these genes represent state markers of the disease: since they are dominant mutations, carriers develop and transmit the disease to 50% of offspring, and penetrance is about 100%. Although ADAD has a rather clear phenotype characterized by memory loss, time and space confusion, apraxia, agnosia, troubles of language, neither the onset nor the phenotype are constant and monomorphic, and overlapping can be frequently observed between clinical phenotypes, genotypes and also pathological proteotypes (Tang et al., 2016). Several families carrying a *PSEN1* mutation have been described with involvement of frontal lobe or spastic paraplegia (Piscopo et al., 2008; Wallon et al., 2012) or extrapyramidal signs thus mimicking Lewy body dementia (Karlstrom et al., 2008; Wallon et al., 2012). Even in the large ADAD Calabrian kindreds, sharing the same *PSEN1* mutation and a classic neuropathological phenotype, at onset symptoms cluster into four different groups: apathetic, amnesic, dysexecutive, disoriented (Bruni et al., 2010) (Fig. 1A). The *APP* A713T mutation leading to AD with cerebrovascular lesions (CVLs) in Calabrian families associates to both early and late onset phenotypes, also independently from homozygosity (Conidi et al., 2015) (Fig. 1B).

The multigenerational ADAD families (Tang et al., 2016) frequently reconstructed along centuries through genealogy with hundreds of affected subjects and at risk relatives represent an extraordinary and powerful model for the study of AD. All the three genes are involved in the processing of β amyloid (Aβ) strongly sustaining the amyloid cascade hypothesis (Schellenberg and Montine, 2012). DIAN cohort constituted by ADAD carriers has already showed that the biological disease starts in the brains decades before clinical onset (Tang et al., 2016) with the deposition of Aβ and the alterations of the other biomarkers. The same certitude cannot be confirmed in late onset AD, that is still unclear regarding etiology and pathogenesis and whose genetic component is complex and much more difficult to ascertain.

The lifetime risk to develop AD is about 10–12% (Breitner et al., 1999) and a genetic susceptibility increasing or decreasing the risk of developing the disease does exist. There is almost an infinite number of susceptibility genes for dementia. The Apolipoprotein E (*APOE*) gene with the ε4 allele gives to carriers a higher risk of developing the disease, especially in women (Liu et al., 2013), shortening the age of onset of AD not only in sporadic AD patients but also in carriers of mutations of both the *PSEN1* (Pastor et al., 2003) and of *APP* (Sorbi et al., 1995). In recent years several whole-genome sequencing studies (GWAS) have suggested that the risk of developing AD is given by the association of common polymorphisms with low penetrance and high frequency in the population and, therefore, with small effect size; although the total number of AD risk genes remains elusive, there is significant evidence suggesting that their combinations may have a substantial impact on disease susceptibility, onset and progression of sporadic late-onset AD (Bertram and Tanzi, 2008).

Theoretically, assessment of genetic risk could be a key to preventing or slowing the progression of the AD. APOE ε4 genotype has been demonstrated as the major predictor of progression to

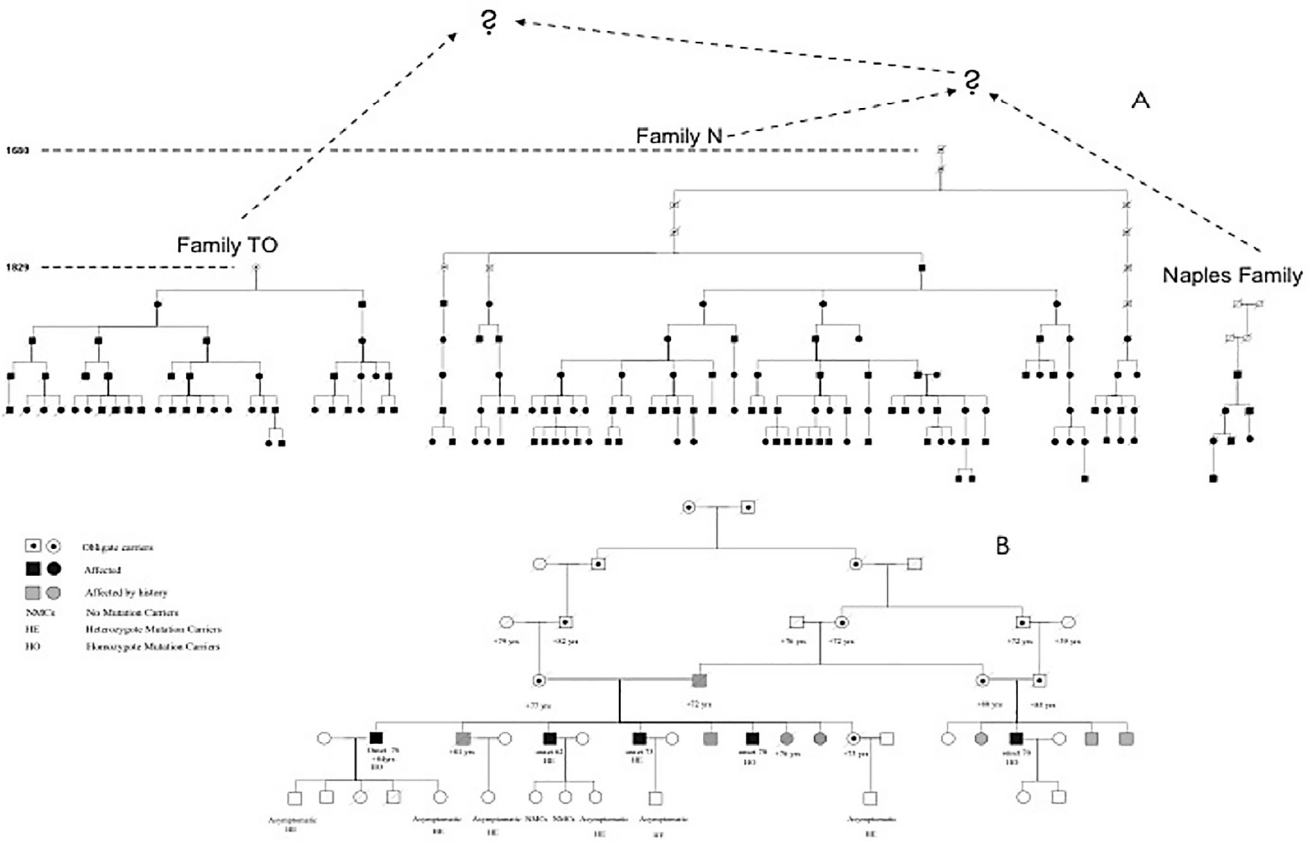


**Fig. 1.** (A) Extended pedigree representing known affected subjects of all families with presenilin 1 (PSEN1) Met146Leu mutation. (B) Pedigree of the family with amyloid precursor protein (APP) A713T mutation associates to both early and late onset phenotypes, also independently from homozygosity.

AD in patients with aMCI (Zheng et al., 2016). However, the use of APOE genotyping is limited due to its low sensitivity and specificity, but it could be useful in combination with other markers including EEG connectivity (Vecchio et al., 2018). Zheng et al. (2016) found a notable increase in plasma homocysteine (HCY) together with a significant decrease in serum brain-derived neurotrophic factor (BDNF) in aMCI-APOE ε4 patients converting to AD. Studies focused on changes in DNA methylation level (i.e. COASY and SPINT1 gene promoter regions) could be helpful to identify subjects destined to progress from MCI to AD (Kobayashi et al., 2016).

Although ADAD mutations are marker of state not of process, combined together with current biomarkers, they will allow an early diagnosis even in the preclinical phase. The implementation and evaluation of AD genetic risk markers in the prediction of MCI to AD dementia progression is in an early phase. However, detecting new susceptibility factors with a functional impact on AD will bring about major insights into the disease pathways, and initiate new lines of research.

### 4.2. Neuropsychological markers

An important milestone for the modern era of AD research is the publication of the NINCDS-ADRDA clinical criteria for the diagnosis of AD, which remained the standard reference in the field for more than two decades (McKhann et al., 1984). According to the original McKhann criteria, "*neuropsychological tests provide confirmatory evidence of the diagnosis of dementia and help to assess the course and response to therapy*". Neuropsychological tests are recommended for specific aims, such as the definition of unusual pattern of cognitive deficits, in the context of longitudinal studies or as outcome measures for drug efficacy trials. An important change took place only in the '90s, with the rise of interest in the identification of a "pre-dementia" stage of AD, resulting in the introduction of the MCI concept (Petersen et al., 1999). Among the criteria for the diagnosis of this at-risk condition for progression to dementia, there is the presence of an objective impairment of memory, defined on the basis of a defective test performance in comparison to an age-matched control group. In the following period this concept was extended, on the basis of the same psychometric criteria, to other cognitive domains besides long-term memory (Petersen, 2004).

The International Working Group Research Criteria (Dubois et al., 2007, 2010, 2014) and the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines (McKhann et al., 2011) introduced a novel approach, based on the concept of an AD continuum, rather than of disease "stages". Both set of criteria emphasize the role of markers in supporting the diagnosis of AD at the very early clinical stages, i.e. when the patient is symptomatic but does not fulfill the criteria for dementia (respectively, *prodromal AD*, or *MCI due-to-AD/prodromal-to-AD*). Within this perspective, neuropsychological tests can be considered as a "gateway biomarker" in the AD diagnostic process (Cerami et al., 2017). In the case of typical presentations of AD, the performance in episodic memory tests is crucial for early diagnosis, and is the basis for the definition of MCI or *prodromal AD* according to current diagnostic criteria. There is however no consensus on the most appropriate tests to be employed. Episodic memory tests are sensitive, but not specific. In addition, they are unsuitable to measure disease severity and progression as they reach floor levels early in the disease course. Tests controlling for effective memory encoding and retrieval may be particularly suit-

able to identify the hippocampal amnestic syndrome, a typical feature of AD "*with the presence of a paradigmatic and specific episodic memory involvement, characterized by a diminished free recall ability, which is only marginally improved by cueing*" (Grande et al., 2018). In this regard, the Free and Cued Selective Reminding Test (FCSRT) has been used to better differentiate the genuine hippocampal deficit of AD from age-associated memory dysfunctions, due to impaired attention, inefficient information processing, and ineffective retrieval (Grober and Buschke, 1987). The FCSRT, as well as the "bedside" 5-Word cued recall test (Dubois et al., 2002; Economou et al., 2016) increase the specificity for AD (Dierckx et al., 2009; Wagner et al., 2012). There is also evidence supporting the value of the FCSRT to predict progression towards dementia in at risk populations (Sarazin et al., 2007).

An important issue is the role of neuropsychological testing in the diagnosis of atypical AD presentations. The three main forms defined by the IGW-2 criteria (Dubois et al., 2014), i.e. the language, visuospatial and behavioral presentations, require specialized neuropsychological assessment for an adequate diagnostic evaluation, in particular in the early stages, for follow-up and for evaluation of treatment effects. The logopenic/phonological variant of primary progressive aphasia (PPA) is by far the most common language presentation of AD (Spinelli et al., 2017). Only very few tools have been specifically developed for the assessment of language deficits in PPA patients, and for the characterization of the PPA subtype, which is relevant for a probabilistic diagnosis of the underlying pathology. The language tests in common use, e.g. Aachener Aphasie Test (AAT) (Huber et al., 1980) and the Boston diagnostic aphasia examination (BDAE) (Kaplan, 1983), have not been specifically developed for the differentiation of the subtypes of PPA, but rather for the evaluation of aphasia due to stroke. A "minimal" procedure, allowing a classification according to the current diagnostic criteria (Gorno-Tempini et al., 2011) must include:

a. a qualitative and quantitative observation of patient's speech and language during a semi-structured interview, which can be based on a complex picture description; the main parameters to be assessed are: lexical production rate and phonological/articulatory errors; disorders of fluency (pauses and repetitions); lexical typology; and syntactic structure and complexity; on this basis, it is possible to conclude for the presence or absence of motor speech disorders and agrammatism, necessary for the differential diagnosis with other PPA variants, seldom associated to AD pathology;
b. tasks of picture naming and word-picture matching to assess single word comprehension;
c. a repetition test allowing an assessment of phonological and auditory verbal short-term memory abilities, typically impaired in logopenic aphasia;
d. sentence-picture matching tasks to assess syntactic comprehension.

The visuo-spatial presentation of AD is posterior cortical atrophy (PCA) (Crutch et al., 2017). This clinical picture is characterized at the onset by prominent visuo-spatial cognitive features, such as deficits in space and object perception, simultanagnosia, constructional dyspraxia, prosopoagnosia, oculomotor apraxia, optic ataxia and alexia. As in the case of logopenic aphasia, all these aspects can be quantified using a wide array of tests, which have been developed for the neuropsychological evaluation of focal brain damage, such as the copy of Rey's figure (Rey, 1941). An excellent screening battery, which allows to evaluate in a short amount of time the function of both ventral and dorsal visual processing pathways is the Visual Object and Space Perception Battery (Warrington and James, 1991).

Finally, a true challenge for neuropsychological assessment is the third variant of atypical AD presentation, characterized by "frontal" features (Ossenkoppele et al., 2015). The crucial issue here is the differential diagnosis with the behavioral variant of frontotemporal dementia, which requires, in addition to biomarker evidence, a detailed neuropsychological assessment. This must not be limited to classical "frontal lobe tests", such as the Wisconsin Card Sorting (Heaton et al., 1993) or the Stroop test (Stroop, 1935), but requires a comprehensive evaluation of behavioral disorders and neuropsychiatric disturbances (for example, with the Frontal Behavioral Inventory, Kertesz et al., 1997, and the Neuropsychiatric Inventory, Cummings et al., 1994), as well as an assessment of social cognition performance (see, for example, Torralva et al., 2009).

To summarize, a clear definition of the cognitive/behavioral phenotype is the first step towards a biomarker-supported pathological diagnosis of AD. The identification of the very early/prodromal stages of both typical (hippocampal episodic memory) and atypical (visuo-spatial abilities, language, executive function and behavior) presentations is one of the main goals of neuropsychological assessment. There is clearly a need for harmonization of tools and procedures and for the collection of high quality psychometric data. This priority, however, should not obscure the importance to develop innovative ideas based on the advances in cognitive neuroscience research. The recent focus on pre-clinical rather than prodromal stages (Dubois et al., 2016) offers a great opportunity for the development of novel, continuous measures assessing cognitive efficiency and functional status. Taking advantage of the technological possibilities, such as those offered by smartphones and social media (Wilmer et al., 2017), is one of the many interesting developments to be explored in the next few years.

### 4.3. Neuroimaging markers

MRI and PET have tremendously improved our diagnostic ability to formulate a correct diagnosis of dementia in clinical settings (McGinnis, 2012). Importantly, these tools have contributed in clarifying the pathophysiology of dementia by providing *in vivo* indirect information on the underlying brain tissue abnormalities.

MRI is a non-invasive tool that allows a detailed anatomical investigation of the brain with an extremely high sensitivity in detecting macroscopic tissue abnormalities (Bozzali et al., 2016).

For this reason, it is routinely used to rule out conditions that may mimic a neurodegenerative form of dementia, such as brain tumors, normal pressure hydrocephalus, subdural hematoma, and cerebrovascular encephalopathy. Conversely, PET imaging detects metabolic brain tissue changes and has proven to be highly sensitive in identifying specific patterns of hypo-metabolism in individuals suffering from degenerative dementia since early clinical stages (Iaccarino et al., 2017). Moreover, new radiotracers have been recently developed to detect peculiar pathological features of neurodegeneration, such as Aβ and tau-protein radiotracers (Jack et al., 2017).

*Conventional MRI.* The main role of conventional MRI, as mentioned above, is that of excluding those conditions that may mimic a clinical presentation of neurodegenerative dementia. Nonetheless, in a proportion of cases, it can provide information to support a correct diagnosis of neurodegenerative dementia based on the identification of peculiar patterns of regional brain atrophy. In clinical settings, visual rating scales can be used to determine the presence of regional patterns of brain atrophy on T1- weighted images (Scheltens et al., 1992; Wahlund et al., 2001). For instance, the "medial temporal lobe atrophy" (MTA) scale has proven accurate in defining the degree of regional atrophy in studies that compared

patients with AD to cognitively intact controls (Ridha et al., 2007). On the other hand, MTA has shown poor sensitivity in quantifying volumetric changes longitudinally (Ridha et al., 2007; Persson et al., 2017). The presence and extension of macroscopic white matter (WM) abnormalities is also a relevant piece of information for the differential diagnosis and staging of dementias. For this reason, *ad hoc* visual rating scales have been developed to quantify the severity of WM lesions on T2-weighted and fluid attenuated inversion recovery (FLAIR) scans. The Age Related White Matter Changes (ARWMC) scale (Wahlund et al., 2001) and the Fazekas' scale (Fazekas et al., 1987) are amongst the most popular, and their use in clinical routine is simple. When a diagnosis of AD is suspected, the combination of the MTA scale with scales assessing WM abnormalities can return abnormal patterns that can be schematically divided in 3 categories: (1) severe MTA and minimal WM changes; (2) minimal MTA and severe WM changes; (3) moderate MTA and moderate WM changes. In case 1, MRI suggests a diagnosis of AD, while in case 2, it supports the hypothesis of a remarkable cerebrovascular contribution to cognitive symptoms. Case 3 is still consistent with the hypothesis of neurodegeneration without a clearcut preference for AD. Moderate MTA in association with moderate WM changes can indeed be seen also in dementia with Lewy bodies (DLB) that, in the absence of Parkinsonism may be challenging differential diagnosis with AD. With respect to WM lesions, especially when present in a moderate degree, an association has been shown with brain amyloid deposition (Marnane et al., 2016), which is characteristic of AD pathology, but which may also coexist with Lewy bodies in in DLB brains.

*Quantitative Brain Volumetrics.* Sophisticated algorithms of image registration have been developed to allow volumetric images from different subjects to be taken into a common space. This advancement in image processing allows between-group comparisons (e.g., patients vs. controls) to be run on a voxel-by-voxel level basis. Additionally, correlations between regional brain volumetrics and clinical, neuropsychological and behavioral measures can be investigated within this same framework. For data-driven analyses, voxel-based morphometry (VBM) is one of the most popular techniques that have been successfully used to investigate dementias (Ashburner and Friston, 2000). VBM is an operator-independent technique that allows the investigation of the whole brain to be run without any need of *a priori* hypotheses on the anatomical distribution of regional brain atrophy (i.e., voxel-wise analysis) (Bozzali et al., 2006). After image normalization, modulation, and segmentation (Ashburner and Friston, 2000), grey matter (GM) maps are extracted and used for statistical group comparisons or for correlations with clinical, neuropsychological and behavioral variables. When used to investigate patients with typical AD at different clinical stages, VBM returns patterns of regional GM atrophy that involve not only the medial temporal lobes but also many other areas of the association cortex (Bozzali et al., 2006; Serra et al., 2010a, 2014). Additionally, VBM has shown meaningful associations between the distribution of regional GM volumes and patients' performance on neuropsychological tests, thus linking together specific patterns of regional GM atrophy with patients' clinical features. (Serra et al., 2010a, 2010b, 2014). As reported before, MCI is a clinical condition associated to an increased risk for developing dementia, and its amnestic form (aMCI) is widely regarded as a prodromal stage of typical AD. Nonetheless, there are other forms of MCI (i.e. non-amnestic MCI, naMCI), whose cognitive profile is dominated by impairments in cognitive domains other than memory. Patients with naMCI are more likely to either convert to a non-typical form of AD or other forms of neurodegenerative dementia. Again, when using VBM to compare patients with aMCI with those with naMCI different patterns of regional GM atrophy can be identified (Serra et al., 2013). At a group level, VBM has demonstrated the ability to discriminate between patients on the transitional stage towards typical AD (i.e., aMCI) from those who are more likely to convert to other forms of dementia (i.e., naMCI) (Serra et al., 2013).

An interesting aspect to be considered in patients with dementia is the so-called "cognitive reserve" (Stern et al., 2018). According to this hypothesis, some individuals are more resilient to the effect of brain damage accumulation thanks to their level of cognitive reserve. When stratifying patients with AD at different clinical stages for their level of cognitive reserve, VBM is able to identify patterns of regional GM volumes that account for the mismatch between clinical disease severity and extension of brain tissue damage in individuals with higher cognitive reserve (Serra et al., 2011).

*Diffusion imaging.* Diffusion imaging measures the microscopic movement of water molecules into the brain, thus providing indirect information on the tissue microstructure/integrity especially within the WM compartment (Basser and Jones, 2002). This technique has been extensively used to investigate patients with AD and MCI (for a review, see Bozzali et al., 2016). Studies using a whole brain approach of image analysis have demonstrated widespread WM alterations in the brain of patients with AD at various clinical stages (Serra et al., 2010a; Liu et al., 2011). Other studies based on diffusion weighted tractography (i.e., a technique that allows the reconstruction of the principal WM tracts) have shown specific patterns of structural disconnection that correlate with patients' clinical stage as well as with some peculiar cognitive deficits (Serra et al., 2012; Bozzali et al., 2012). For instance, an investigation focusing on the cingulum (i.e., the main pathway of connection between the medial temporal lobe structures and the rest of the brain) has demonstrated a progressive loss of structural integrity of this WM tract over the transition from normal aging to AD passing through the preclinical stage of aMCI (Bozzali et al., 2012). Interestingly, this microstructural WM damage together with the regional GM atrophy predicts the level of cognitive impairment at both disease stages, aMCI and AD (Bozzali et al., 2012). A novel method of diffusion imaging analysis, called anatomical connectivity mapping (ACM), has been proposed to assess the structural brain connectivity into the whole brain tissue (Bozzali et al., 2011, 2013). This approach has highlighted not only patterns of structural brain disconnection over the transition from normal aging to AD, but also possible mechanisms of brain plasticity (Bozzali et al., 2011, 2013).

*Functional MRI.* Neuronal activity can be indirectly assessed *in vivo* through blood oxygenation level dependent (BOLD) functional MRI (fMRI). fMRI is used to investigate the patterns of brain activation in subjects who are requested to perform various types of task, including those engaging higher level abilities (e.g., memory, visuo-spatial attention, executive functions, emotion processing, etc). Another way to use fMRI for brain investigation is collecting a time series of BOLD volumes at rest in the so-called resting-state fMRI technique. Resting-state fMRI aims at detecting coherent fluctuations of brain activity over time that allow the assessment of functional brain connectivity, and its changes as a consequence of brain diseases. Functional brain connectivity can be assessed within specific networks, some of which have been associated with specific cognitive functions.

Task-driven fMRI investigations to assess the neurobiological changes related to episodic memory deficits in patients with AD have demonstrated reduced activity in the hippocampus and other temporal lobe areas, and increased activity in the parietal association cortex (Peters et al., 2009). Other studies based on memory tasks have demonstrated decreased brain activation not only in the temporal lobe structures but also in parietal and frontal regions (Golby et al., 2005). Most studies involving patients with MCI have shown patterns of increased activity within brain regions related to the specific cognitive tasks (for a review, see Pihlajamäki et al.,

2009). An explanation for this increased task related brain activation at early AD stages is that it might represent a compensatory mechanism against the accumulation of brain damage (Lenzi et al., 2011).

When using resting-state fMRI there are several networks that can be investigated. Amongst them, the so-called default-mode network (DMN) (Greicius et al., 2003) has proven being the most targeted one by AD pathology. This network includes the posterior cingulate cortex, the inferior parietal and the medial prefrontal cortex. A study that combined resting-state fMRI and VBM to assess respectively changes in functional brain connectivity and regional GM atrophy demonstrated, in patients with MCI and AD, that functional disconnection precedes the accumulation of GM atrophy in the posterior cingulate cortex (Gili et al., 2011). The posterior cingulate cortex, which is one of the key nodes of the DMN, is structurally connected to the medial temporal lobes through the cingulum (Bozzali et al., 2012). This supports the hypothesis that, at least in some brain regions such as the posterior cingulate, brain atrophy may be caused by disconnection mechanism (Gili et al., 2011). Moreover, DMN connectivity within the posterior cingulate cortex has been found to be modulated by individual levels of cognitive reserve (Bozzali et al., 2015). This contributes to our understanding of the possible mechanism by which cognitive reserve operates in delaying the clinical impact of AD pathology. A more sophisticated way to analyze resting-state fMRI data is based on the use of brain connectomics. When assessing the modulation of cognitive reserve on brain connectomics in patients with MCI and AD, such an effect is observed in the former but not in the latter patient group (Serra et al., 2017). Indeed, MCI patients with higher levels of cognitive reserve revealed an increase of functional connectivity in their fronto-parietal nodes and a decrease of connectivity in in their fronto-temporo-cerebellar nodes (Serra et al., 2017). The absence of such a modulation in AD patients suggest that cognitive reserve acts to counterbalance the clinical symptoms of AD in an earlier time window of the transitional stage towards dementia. This has implications for pharmacological and non-pharmachological interventions (Koch et al., 2018) in AD patients.

*Metabolic Imaging.* PET imaging has shown the ability to detect pathological brain abnormalities in the absence of detectable changes on MRI (Phelps, 2000). $^{18}$Fluorodeoxyglucose ($^{18}$FDG-PET) is a widely available radiotracer that provides information on regional brain glucose metabolism (i.e., a proxy measure of neuronal activity) (Bohnen et al., 2012). The pattern of hypometabolism that is typically detected by $^{18}$FDG-PET in patients with AD involves the temporo-parietal association cortex, the precuneus and the posterior cingulate cortex (Iaccarino et al., 2017; Bohnen et al., 2012; Kato et al., 2016). $^{18}$FDG-PET has proven highly sensitive and specific in identifying patients with AD from healthy elderly individuals (sensitivity ranging from 70 to 90%) as well as from patients suffering from other forms of neurodegenerative dementia (specificity of 87%) (Knopman, 2012).

More recently, amyloid PET imaging has been introduced to detect the presence of AD pathology *in vivo* (Rowe and Villemagne, 2013). The idea is that an abnormal processing of Aβ peptides triggers some critical pathophysiological events that eventually result in accumulation of Aβ plaques in the brain tissue (Hardy and Selkoe, 2002). This process is known to occur many years before the clinical onset of AD.

Within such a pathophysiological framework, amyloid PET imaging has shown the ability to detect, in patients with AD, an increase of tracer binding in medial frontal and orbitofrontal areas, in the lateral parietal and temporal cortex, in the precuneus and posterior cingulate cortex (Rowe and Villemagne, 2013). These anatomical regions are well known to exhibit a high concentration of Aβplaques in AD brains. On the other hand, amyloid PET imaging has shown some limitations when used in clinical settings. Aβ brain deposition is indeed widely present also in cognitively normal individuals, and discriminating between normal aging abnormalities and AD pathology can be particularly challenging, especially in cases of late-onset AD.

With respect to the prognostic value on the risk of conversion to AD, $^{18}$FDG-PET and amyloid PET imaging have both proven highly powerful techniques. When using $^{18}$FDG-PET and amyloid PET imaging in combination, the former has resulted being the best individual predictor of AD conversion (Iaccarino et al., 2017).

Finally, PET imaging is still in continuous evolution. There are other radiotracers available to target *in vivo* other aspects of neurodegeneration, such as the brain accumulation of tau protein (Jack et al., 2017).

### 4.4. Fluid markers

In the last two decades, several fluid markers, both for specific and non-specific pathologic changes in AD patients, have been proposed and tested. Over time, the most consistent findings have been obtained with three CSF markers: the Aß$_{1-42}$ peptide (Aß$_{42}$), the total tau protein (T-tau) and the phosphorylated tau protein (P-tau) (Blennow et al., 2006, 2010). Although CSF contains less protein than serum, "*CSF markers are preferred over blood/plasma biochemical markers to reflect brain pathophysiology in AD for two main factors: 1) the direct contact between the brain and the CSF characterized by a boundless bi-directional flow of proteins and 2) the presence of the blood-CSF barrier that shields the CSF from direct impact of the peripheral system through a restricted transportation of molecules and proteins*" (Olsson et al., 2016). Indeed, the three CSF markers are related to the three main pathological changes that occur in the AD brain: amyloid deposition in Aß plaques, intracellular neurofibrillary tangles (NFT) formation, and neuronal loss. Particularly, in AD patients, Aβ42 is found at low concentrations due to cortical amyloid deposition, T-tau at high concentration due to cortical neuronal loss, and P-tau at high concentrations, reflecting cortical tangle formation: this pattern is commonly referred to as the "AD signature" (Galasko et al., 1998; Clark et al., 2003; de Leon et al., 2006; Fagan et al., 2007, 2011; Shaw et al., 2009).

There are numerous reviews on the diagnostic value of the CSF markers, including in the early stages of AD (for a recent review see Olsson et al., 2016). In particular, the combination of these CSF markers increases the diagnostic accuracy with sensitivity and specificity reaching 85–90%, both for early identification of AD and for distinction between AD and non-AD dementias (Blennow et al., 2010). The CSF markers are also highly predictive of progression to AD from MCI (Hansson et al., 2006; Fagan et al., 2007; Li et al., 2007; Diniz et al., 2008; Brys et al., 2009; Mattsson et al., 2009; Snider et al., 2009; Shaw et al., 2009). Subsequently, the diagnostic criteria for AD dementia established by the NIA-AA (McKhann et al., 2011) and the research criteria by the IWG-2 (Dubois et al., 2014) recommend the use of fluid markers (reduced levels of Aβ42 and elevated levels of T-tau and P-tau in CSF), when there is a need to increase the certainty that the underlying cause of a dementia syndrome is AD. Similar recommendations for markers were presented in the most recent European Federation of Neurological Societies guidelines for the diagnosis and management of AD (Hort et al., 2010) and other dementias (Sorbi et al., 2012). In the diagnostic criteria for MCI *due-to-AD* developed by NIA-AA, a positive Aß marker (either by amyloid-PET or CSF) together with the presence of a neuronal injury marker, such as medial temporal lobe atrophy or elevated levels of T-tau and P-tau in the CSF indicates that the MCI syndrome may be because of AD, whereas negative Aß markers suggest that MCI is unlikely because of AD (Albert et al., 2011). The IWG-2 criteria for *prodromal AD* are the presence

of episodic memory decline of the hippocampal type as the leading clinical symptom and positive marker evidence from either CSF or imaging that supports the presence of underlying AD pathology (Dubois et al., 2014). Although such bulk of evidences, further research, validation, and standardization are required for a clinical routine use (for recent recommendations about the use of CSF markers in clinical practice see Herukka et al., 2017, and Simonsen et al., 2017).

In addition to the classical CSF markers, other candidate markers from alternative non-invasive matrices, particularly blood, have been investigated and are currently under study. Meanwhile, they are presently less considered in International Guidelines than CSF markers. In fact, data available in literature on plasma markers show conflicting results (for a review see Olsson et al., 2016), so that their use for the diagnosis of AD is not yet validated. For example, merely reporting main findings for the classical AD markers, blood $A\beta_{42}$ level has been found to be unchanged or having only small variations in AD group respect to control (Olsson et al., 2016). On the same line, different studies found an increase, a decrease or no changes of plasma tau levels in AD patients (Sparks et al., 2012; Chiu et al., 2013, 2014; Tzen et al., 2014; Wang et al., 2014). Conversely, interesting results have been found investigating blood levels of neurofilament light protein (NFL), a marker of axonal damage, which resulted increased in both MCI and AD patients respect to controls and showed a correlation with CSF concentration and with cognitive impairment (Lewczuk et al., 2018). Other similar emerging blood markers, linked to phenomena like neurodegeneration (neuron-specific enolase, NSE, and heart fatty acid binding protein, HFABP), Aβ metabolism (Aβ40), tangle pathology (P-tau), glial activation and inflammatory response to the disease (glial fibrillary acidic protein, GFAP, and monocyte chemotactic protein 1, MCP-1), have been tested with variable results. Most of them show a significative correlation with the AD disease in CSF concentrations, but the corresponding plasma levels do not seem to reflect such modification (Olsson et al., 2016). In any case, the identification of reliable blood markers – both classical and emerging – is challenging because traditional immunoassay platforms do not have a high sensitivity in detecting specific brain pathological markers in a matrix like plasma, in which the great number of cells and different classes of molecules determine a potential analytical interference. To avoid this limit, novel ultrasensitive approaches and techniques are emerging – such as mass-spectrometry analysis (MS) (Nakamura et al., 2018), immunomagnetic reduction (IMR) (Yang et al., 2017), electrochemiluminescence (ECL) and the single molecule array (SIMOA) (Kuhle et al., 2016) –, with the purpose of increasing accuracy and sensitivity of the detection. At this regard, standardization and quality control programs, aimed to the definition of standard operating methods and analytical procedures, are mandatory to warrant the application of blood and CSF markers for both clinical trials and routine clinical diagnosis of AD.

## 5. EEG markers

The human brain can be imagined as a gigantic anatomo-functional scaffold modeled by myriads of network structures at micro-meso-macro-scale levels, with nodes and links that dynamically cooperate with time-varying aggregations via transient and rapid locking/unlocking of the orchestrated firing synchronization of spatially separated neuronal assemblies (Singer, 1990; Jung et al., 2001; Makeig et al., 2002; Fuentemilla et al., 2006). Both Internal and external inputs from the surrounding environment and learning/training and aging process continuously continually interfere with the remodeling of brain networks throughout life via plastic mechanisms mainly utilizing the Long Term Potentiation/Depression (LTP/LTD) mechanisms of synaptic transmissions.. Network configuration and excitability also fluctuate in millisecond time frames, according to the cyclic changes of the cortical state (“cortical uncertainty,” Adrian & Moruzzi, 1939), with an impact on their instantaneous efficacy for a given task’s performance. “*Such phenomena are reflected in the overall electromagnetic brain signals oscillating at various rhythms, which are recordable from the scalp via electroencephalography (EEG) and magnetoencephalography (MEG); “phase synchronization (or coherence), phase-locking, entrainment, cross-frequency (or power synchrony), and phase reset of EEG rhythms measure the degrees of functional connectivity between different brain areas and play a key role in the fluctuating cortical state, reflecting communication across spatially separate functional regions operating at different frequencies and cross-frequency synchronies*” (Buzsaki, 2005; D’Amelio and Rossini, 2012; Vecchio et al., 2019a,b). EEG and MEG record time-varying changes of electromagnetic signals with a time resolution of milliseconds and follow the dynamics and hierarchies of neuronal assembly connection/disconnection; these synchronization mechanisms are also linked with performance in cognitive functions (Uhlhaas and Singer, 2006; Buzsaki and Schomburg, 2015).

Scalp resting state EEG rhythms reflect the summation of oscillatory membrane post-synaptic potentials generated from cortical pyramidal neurons, which play the role of EEG sources. Based on biophysical considerations, these sources were estimated as extended several squared centimeters (Nunez and Srinivasan, 2006; Srinivasan et al., 2007). These potentials can be considered as the oscillatory output of the resting state cortical system, while inputs were afferents coming from other cortical neural biomasses and thalamo-cortical neurons and neurons belonging to ascending reticular systems (Nunez and Srinivasan, 2006).

In clinical neurophysiology, frequency analysis of scalp EEG rhythms reveals most spectral content under 50 Hz in standard physiological conditions as scalp and skull do act as spatial and frequency filters. Indeed, EEG rhythms can be investigated at higher frequency bands, e.g. 100–250 Hz, using intracranial or MEG recordings that eliminate the skull filtering effects. In an ideal spectral analysis of scalp EEG rhythms, frequency bands of interest should be related to peaks in power density spectrum to denote relevant neural process (Lopes da Silva, 2013).

Linearity and non-linearity is the behavior of a neural circuit, in which the output signal strength varies in direct or non-direct proportion to the input signal strength respectively. Herein we used the term “synchronization” to denote non-linear oscillatory components of the brain system as a reflection of a collective oscillatory behavior of cortical neural populations generating EEG rhythms (Boccaletti et al., 2002). To produce scalp EEG rhythms, this “synchronization” mechanism must occur at a macroscopic spatial scale of some centimeters. Synchronizing neural populations in the cerebral cortex are the main source of scalp EEG rhythms.

Typical linear characteristics of scalp EEG rhythms are power density/amplitude and phase. Magnitude and topography of power spectral density computed from scalp EEG rhythms is the most used marker of cortical neural synchronization. It is often computed by Fast Fourier Transform (FFT). Alternative advantageous procedures use parametric autoregressive models and wavelets analysis.

Spectral analysis of EEG rhythms is typically done at fixed frequency bands. There is a promising convergence of spectral analysis results of EEG rhythms in patients with AD. Compared to seniors with intact cognition (Nold), these patients show widespread increase in δ and θ power density and posterior decrease in α and β power density with frequency lowering of α power density peak (Jelic et al., 2000; Adler et al., 2003; van der Hiele et al., 2007; Nishida et al., 2011; Scheeringa et al., 2012). Non-linear

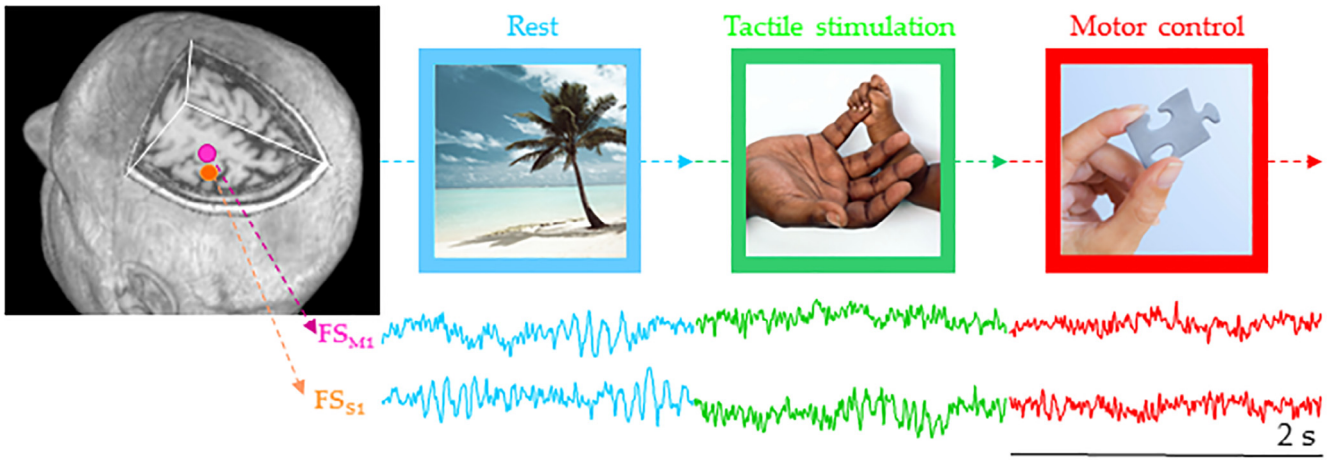


**Fig. 2.** The Functional Source Separation (FSS) algorithm is a new concept-source identification method with Magnetoencephalography (MEG)/Electroencephalography (EEG)/Electromiography (EMG), developed by LET'S. To identify the source, FSS exploits a specific functional fingerprint of the source neurodynamics -instead of the source's position-. FSS returns the source's neurodynamics in all experimental conditions of interest, together with the source scalp distribution, which is the input for the localization algorithms, if the source's position is of interest.

measures of "synchronization" markers pointed to a complexity loss of cerebral dynamics in AD in the same frequency bands (Pritchard et al., 1994; Woyshville and Calabrese, 1994; Besthorn et al., 1995; Stam et al., 1995, 1996; Jelles et al., 1999; Dauwels et al., 2010a; Azami et al., 2017a for a review).

Scalp topography of EEG rhythms reflects the summation of EEG activity generated by frontal, parietal, occipital, and temporal source activities with poor spatial resolution of several centimeters. Compared to scalp EEG mapping, EEG source estimation presents the advantage that the cortical generators of EEG activity may be approximately disentangled. Of note, EEG source estimates are approximations of intracerebral neural current flows.

Both non-linear and linear mathematics can estimate neural current density of EEG cortical sources (Valdés-Sosa et al., 2009; Gramfort et al., 2013). These procedures model 3D tomographic patterns of EEG cortical generators into a spherical or an MRI-based head model representing electrical properties of cerebral cortex, skull, and scalp, typically co-registered to Talairach brain atlas (Talairach and Tournoux, 1988; Yao and He, 2001; Pasqual-Marqui, 2002, 2007a, 2007b). Source localization procedures estimate the current intensity of all dipoles (e.g. hundreds to thousands) of cortical model to explain scalp EEG amplitude/power density. These solutions are mathematically regularized to account the fact that the EEG inverse problem is under-determined and ill-conditioned.

An important step in EEG analysis is to maximize the signal-to-noise ratio by trying to separate, as much as possible, the signal from the noise using information on the specific source under study. In some cases, it is possible to observe neural activity synchronization by supplying to the subject an external stimulus, or instructing the subject to perform a specific task. Asking to repeat this task many times and triggering the onset of analysis on the task onset, an average may be obtained over all the epochs. In this way, only the electromagnetic field originated by a source time-and-space correlated with the task is left unchanged, while all other signals are reduced by a factor $1/\sqrt{N}$, where N is the number of averages.

Given the high relevance of analyzing resting state activity, alternative procedures to enhance the signal to noise ratio were developed including Blind Source Separation (BSS) methods such as Independent Component Analysis (ICA) (Hyvarinen et al., 2001) and semi-BSS methods such as Functional Source Separation (FSS) (see Fig. 2) (Tecchio et al., 2007; Porcaro and Tecchio, 2014).

A relevant step relates the determination of the current density distribution inside the brain, especially in some region of interest. The diverse approaches to solve the so-called inverse-problem range from single and multiple dipoles (Scherg and Berg, 1991) to distributed sources, which include the Multiple Signal Classification (MUSIC) (Mosher et al., 1992), the recursively applied and projected-MUSIC (RAP-MUSIC) (Mosher and Leahy, 1999), the minimum norm estimates (MNE) (Hämäläinen and Ilmoniemi, 1994) and the Low resolution brain electromagnetic tomography (LORETA) (Pascual-Marqui et al., 1994). Furthermore, spatial filtering procedures, like beam forming, for example synthetic aperture magnetometry (SAM) (Vrba and Robinson, 2001), are also alternatives.

Given the side effects in solving the inverse problem, which depends on biophysical properties external to EEG-MEG information and in part unknown (proper conductivity of diverse extracerebral tissues), neuroscientific community spends huge efforts to extract the information of interest from the identified sources derived from BSS and semi-BSS methods.

In both cases stronger analysis tools exploits graph theory (Miraglia et al., 2017), which returns indicators of the balance between the local connectedness and the global integration of a network mainly concentrating the evaluation on the connectivity features of the involved regions. Approaches concentrating on the dynamic features of the neuronal activity include the power estimate in diverse oscillatory frequency ranges and non-linear measures assessing either the complexity of the signal (Escudero et al., 2015) or its fractal dimension (Smits et al., 2016).

## 6. The relevance of EEG in AD investigation

### 6.1. Resting-state EEG

There is a vast literature on EEG abnormalities in pathological brain aging (for a review see Rossini et al., 2006). Compared to Nold subjects, AD patients contain excessive $\delta$ and a significant decrement of posterior $\alpha$ rhythms (Huang et al., 2000). Similarly, MCI display a significant decrease of $\alpha$ power compared to Nold (Koenig et al., 2005). Furthermore, a prominent decrease of EEG spectral coherence in $\alpha$ band in AD has been reported (Jelic et al., 2000; Adler et al., 2003).

The EEG $\theta$ power was found to be higher in aMCI who will convert to AD. In fact, a high predictive accuracy of baseline EEG fea-

tures for predicting future decline was found (Prichep et al., 2006). Furthermore, the analysis of EEG coherence (the phase different of the oscillations of a given frequency at two different electrodes) has been shown to contribute to the differentiation of AD from Nold (Adler et al., 2003) and to the prediction of aMCI conversion to AD (Jelic et al., 2000). However, findings were usually significant only at a group level (de Haan et al., 2012a); moreover, relatively small samples were investigated with a briefer than required follow up. Despite such limitations, an important review (Dauwels et al., 2010a) has summarized the progresses in the diagnosis of AD: generalized slowing of the spectral profile, reduced complexity and perturbations in EEG.

Similar features of EEG sources with some attenuation in amplitude seen in AD patients were also observed in MCI subjects (see Canuet et al. 2012; Babiloni et al., 2016). These findings were confirmed by an independent approach based on minimum-norm depth-weighted estimation (Hsiao et al., 2013). Relative to aMCI subjects, AD patients pointed to reduced activity in precuneus, posterior cingulate, and parietal regions as well as increased activity in δ or θ sources in inferior parietal, medial temporal, precuneus, and posterior cingulate (Hsiao et al., 2013).

Cross-validation of EEG source solutions was successfully done with correlation study with patients' clinical/cognitive status and other AD markers. In AD subjects, clinical symptoms were positively correlated with abnormalities in β, α, and δ source activities (Dierks et al., 1993; Babiloni et al., 2009). Global cognitive status as revealed by MMSE score correlated negatively with δ/θ source activity and positively with α source activity (Gianotti et al., 2007; Babiloni et al., 2011a,b, 2013, 2015; Canuet et al., 2012).

Occipital, temporal, and parietal α source activity was maximum in aMCI patients with greater hippocampal volume, while they were intermediate in those with smaller hippocampal volume, and minimum in AD patients (Babiloni et al., 2009). In addition, widespread α source activity was positively related to the volume of cortical gray matter in aMCI and AD subjects, while a negative correlation was found with widespread activity in δ sources (Babiloni et al., 2013). In these subjects, there was a positive correlation between occipital-parietal α source activity and corresponding gray matter volume (Babiloni et al., 2015). Moreover, it was shown a negative correlation between EEG α dipolarity (e.g., uniformity of alpha potential distribution) and P-tau or T-tau/Aβ in cerebrospinal fluid in AD (Kouzoki et al., 2013).

### 6.2. Event-related potentials

Event-related potentials (ERPs) are brain potentials time-locked to a sensory, cognitive, or motor event (Blackwood and Muir, 1990; Luck, 2014). Usually, ERPs are recorded by averaging several brain responses over a large number of experimental trials in order to boost signal-to-noise ratio. The resulting waveforms reflect the occurrence of sensory and cognitive processes in the brain, providing information about both the time course of the event (with a high resolution) and the spatial disposition of generating sources. Therefore, ERPs allow studying neural correlates of information processing related to sensory-motor, perceptual and higher cognitive functions (Howe et al., 2014).

The great majority of works about ERPs focused on the analysis of P300 component that is the most extensively used in clinical applications to study dementia and aging. P300 is a scalp-positive ERP component with a peak around 250–500 ms and an amplitude of 10–20 μV elicited by auditory, visual, or somatosensory stimuli (Polich and Kok, 1995). For its evaluation, the so-called "oddball" paradigm is commonly used, in which there is an alternation of frequent and irrelevant (standard/non-target) stimuli and of random, infrequent and task-relevant (target) stimuli that have to be detected (Polich and Criado, 2006; see Rossini et al., 2006 for a review). While P300 amplitude seems to reflect memory processes and especially attentional abilities during task execution (Gonsalvez and Polich, 2002), its latency seems to be linked to the stimulus more than the response processing and is generally independent of behavioral response time (Duncan-Johnson, 1981; Verleger, 1997; Ilan and Polich, 1999). Therefore, in clinical settings, peak latency has been used as a motor-free measure of cognitive function, showing a negative correlation with mental function in normal subjects: in fact, shorter latencies are associated with high cognitive performance in attention and immediate memory tasks (Polich et al., 1983, 1990; Polich and Martin, 1992; Stelmack and Houlihan, 1994; Reinvang, 1999), while increased latencies are found both in normal aging and further in dementia (Polich et al., 1986; Fjell and Walhovd, 2001;Polich, 1997).

In general, almost all previous P300 studies reported a prolonged latency in AD patients compared to age-matched healthy controls (Pedroso et al., 2012), with a particular sensitivity for deterioration of language, memory, and executive functions (Lee et al., 2013). Two recent meta-analyses demonstrated that P300 latency could reliably distinguish groups of MCI patients from controls (Howe et al., 2014; Jiang et al., 2015). Moreover, Jiang et al. found that stable MCI patients showed a shorter P300 latency and larger amplitude compared to MCI *prodromal-to-AD* patients (Jiang et al., 2015). Although the majority of P300 studies in AD focused on its latency, changes in its amplitude have also been found (Parra et al., 2012; Hedges et al., 2016) with sensitivity and specificity above 80% (Juckel et al., 2008).

Concerning other types of ERPs evidence shows that early components are usually less affected in AD, while later potentials, because they probably refer to higher cognitive processes, could be more effective to evaluate the progression of cognitive decline: in fact, in the early stage of the disease a decreased P600 and N400 repetition effect and also a delayed N200 latency can be usually detected, thus providing an useful marker to predict the conversion from MCI to AD (Horvath et al., 2018).

Finally, it is noteworthy to highlight that the diagnostic validity of ERPs is considered relatively poor, essentially because of the great variability of sensitivity and specificity of ERPs measurements reported in the literature. Hence, although recent studies using promising clinical ERPs approaches presented prediction accuracies of MCI/ AD progression in the 85–95% range (Bennys et al., 2007; Olichney et al., 2008; Chapman et al., 2011), and besides their theoretical interest, it is urgently necessary a standardization of ERPs assessment procedures in order to encourage their inclsusion in clinical routine.

### 6.3. Event-related synchronization/desynchronization

In the analysis of ERPs, the early and late positive and negative potentials were studied in the time domain as the components named N100, N200, P200, P300, late positive potential, etc. ERPs do not just have time-related changes, but these potentials also have frequency content properties. It is possible to analyze the frequency specific changes related to the function by different methodologies. The main aim in the analysis of frequency-specific changes is to find out the increase or decrease of the power spectrum in a specific frequency band and to find out phase information of this frequency band related to the given stimulation/task. Event-related increase in a specific frequency band is called Event-Related Synchronization (ERS) whereas event related decrease in a specific frequency is called Event-Related Desynchronization (ERD). ERS/ERD analysis was first introduced by Pfurtscheller and Aranibar (1977) and by Pfurtscheller and Lopes da Silva (1999). Klimesch (1999) reported that event-related upper α ERD is positively correlated with long-term memory performance, whereas an increase of θ ERS is positively correlated with

**Table 1**
Summary of the time-frequency dynamics of AD and MCI patients in the literature.

| Frequency | Delta response | Theta response | Alpha response | Beta response | Gamma response |
|---|---|---|---|---|---|
| AD | ↓ Decreased delta ERS | ↓ Decreased theta power/ ERS, decreased theta phase locking | ↓ Decreased ERD<br>↑ Increased ERD | ↓ Decreased, beta power/ERS<br>↓ Decreased beta ERD | ↓ Decrease early gamma ERS,<br>↑ Increased Gamma power<br>↓ Decreased gamma ERD |
| MCI | ↓ Decreased delta ERS | ↓ Decreased theta power/ ERS, decreased theta phase locking | ↓ Decreased alpha phase locking | ↓ Decreased, beta power/ERS<br>↓ Decreased, beta phase locking ↓ Decreased beta ERD | |
| References | Caravaglios et al. (2008)<br>Kurt et al. (2014)<br>Yener et al. (2008, 2012, 2013)<br>Yener and Başar (2013) | Caravaglios et al. (2008)<br>Cummins et al. (2008)<br>Deiber et al. (2009, 2015)<br>Yener et al. (2007) | Babiloni et al. (2000, 2005)<br>Deiber et al. (2015)<br>Fraga et al. (2017)<br>Karrasch et al. (2006) | Deiber et al. (2015), Fraga et al. (2017)<br>Güntekin et al. (2013), Kurimoto et al. (2012)<br>Missonnier et al. (2007) | Başar et al. (2016),<br>Osipova et al. (2006)<br>van Deursen et al. (2011)<br>Kurimoto et al. (2012) |

AD: Alzheimer's Disease. MCI: mild cognitive impairment. ERS: event-related synchronization. ERD: event-related desynchronization. MCI: mild cognitive impairment.

the encoding of new information. Başar (1980) on the other hand mainly focused on the event-related increase of responses in a specific frequency band and called these responses as Event Related Oscillations. Furthermore, the role of pre-stimulus activity to post-stimulus responses both by analysis of power and phase information of the signal were shown (Başar, 1998, 1999) and the dynamics of event-related oscillations and the evoked power spectrum, digital filters, phase locking factors and event-related coherences for a specific function were explored in detail. Delorme and Makeig (2004) proposed their open toolbox to analyze ERS and ERS and as well as the inter-trial coherence, which is a measure of phase locking factor. During the analysis of time and frequency changes of ERPs, it is crucial to analyze all frequency bands with taking into consideration the change of event-related power spectrums and phase locking factors. In the last decade, researchers analyzed event-related time-frequency dynamics to find out the electrophysiological markers for AD. Table 1 represents the event-related time-frequency dynamics of AD patients.

*Event-Related δ Responses:* a decrease of digitally filtered δ responses is found in AD patients in comparison to healthy controls. Several researchers showed increased δ response correlated with the increased cognitive load (Güntekin and Başar, 2016). In AD, the differentiation between "target" and "non-target" responses in δ response was not found as in controls, but there was a δ response decrement during both visual and auditory oddball paradigms (Caravaglios et al., 2008; Yener et al., 2008, 2012). Furthermore, the decrease of δ response was correlated with the decrease of frontal brain volume (Yener et al., 2016). MCI patients had also decreased δ responses during "oddball paradigm" (Kurt et al., 2014; Yener et al., 2013). Furthermore, there was a gradual decrease in δ responses being higher in healthy elderly controls, lower in MCI and lowest in AD (Yener and Başar, 2013).

*Event-Related θ Responses:* θ responses are mainly increased in frontal-central areas during cognitive paradigms. θ ERS is positively correlated with the encoding of new information (Klimesch, 1999) and increased θ power and θ phase locking was observed during working memory paradigms (Klimesch et al., 1997; Başar et al., 2001; Sauseng et al., 2010). AD and MCI patients had abnormalities in θ response due to their cognitive decline (Cummins et al., 2008; Deiber et al., 2009, 2015). Deiber et al. (2009) showed that progressive MCI had reduced baseline induced θ power than stable MCI and healthy controls during N-back task. In a recent study Deiber et al. (2015) reported decreased θ ERS in MCI patients in comparison to healthy controls. Caravaglios et al. (2010) showed that AD patients had increased prestimulus θ activity and reduced event-related θ power in comparison to healthy controls during auditory oddball paradigm. θ-γ coupling during working memory paradigms also merits special attention: Goodman et al. (2018) analyzed θ-γ coupling in patients with MCI and AD during N-back working memory task. Authors showed that healthy controls had higher θ-γ coupling on the 2-back working memory task, on the other hand, MCI patients and AD patients had impaired θ-γ coupling and AD patients had the lowest θ-γ coupling in comparison to all other groups.

*Event-Related α Responses:* α response has an important role in sensory, cognitive and memory processes (Klimesch, 1999). Although Klimesch's inhibition theory had high acceptance in the research area, many studies are showing that increase of α response and/or α ERS has essential functional correlates, including sensory and memory functions (for a review see Başar, 2012; Başar and Güntekin, 2012). α ERD was reduced in healthy aging subjects (Gevins et al., 1997; Gevins and Smith, 2000). Babiloni et al. (2000) during movement related task showed an abnormal preponderance during both movement related β ERD, post-movement β and α ERS values in AD. In a MEG study, Babiloni et al. (2005) reported delayed α ERD latency and increased α ERD peak in patients with dementia in comparison to healthy young and elderly subjects during the visual delayed choice reaction task. On the other hand, Karrasch et al. (2006) found reduced ERD in AD patients during auditory-verbal Sternberg memory task. In a recent study, Fraga et al. (2017) also reported decreased α ERD in patients with MCI and AD in comparison to healthy controls during N-Back task. To our knowledge there is only one study that analyses event-related phase locking α responses in MCI(Deiber et al., 2015) that showed decreased α phase locking in MCI patients in comparison the healthy controls. New researches with including large patient groups are needed for understanding the dynamics of α responses in AD patients.

*Event-Related β Responses:* β responses are mainly related to sensory-motor functions, being these responses depressed during voluntary movement and motor imagery. However, the researches performed in the last decade have shown that β responses are also related to cognitive and working memory functions (Tallon-Baudry et al., 1998; Güntekin et al., 2013; Onton and Makeig, 2009; Ravizza et al., 2005). Missonnier et al. (2007) found that β ERS was lower in progressive MCI and AD in comparisons to stable MCI and healthy controls during attentional detection task. Güntekin et al. (2013) showed that healthy controls had higher β phase locking and power during target stimulation in comparisons to "non-target" simulation, whereas this was not the case for MCI patients who had reduced β phase locking and power during auditory oddball paradigm. Deiber et al. (2015) had also showed reduced ERS and β phase locking in MCI patients in comparisons to healthy controls during N-Back task.

*Event-Related γ Responses:* Evoked and induced γ responses play an important role both in sensory and cognitive processes. The increase of γ responses was reported during increased attention, memory processes, face and emotional picture recognition (Başar-Eroglu et al., 1996; Keil et al., 1999; Singer, 1999; Tallon-Baudry and Bertrand, 1999; Herrmann et al., 2004; Jensen et al., 2007; Başar, 2013; Güntekin and Başar, 2014). Osipova et al. (2006) and Van Deursen et al. (2011) found increased γ responses in AD patients in comparison to healthy controls during auditory steady-state responses. Kurimoto et al. (2012) analyzed the ERS/ERD in AD patients during Sternberg paradigm and reported that AD patients had reduced γ ERD. On the other hand, Başar et al. (2016) analyzed the filtered γ responses in three different sub-frequency γ bands and four different time windows during visual oddball paradigm. These authors found that healthy controls had higher γ responses during 0–200 ms in comparison the AD patients, whereas AD patients had higher late γ responses. Both sensory and cognitive paradigm elicits early γ phase locking. Differentiation between sensory and cognitive paradigms was found in later time windows (200–400 ms and 400–600 ms) (Başar et al., 2015). Therefore, the γ responses should be analyzed in different time and frequency windows. Analysis of ERD/ERS and phase locking of γ responses in AD patients during different sensory and cognitive paradigms are still needed to see the differentiation of γ responses in AD patients and healthy controls. Early and late γ responses should be analyzed separately to find out the differentiation of γ responses in AD patients comprehensively.

### 6.4. Attention and working memory-related EEG features

EEG signals associated with selective attention and working memory may detect very early and subtle changes in cortical network function at baseline in cognitively intact elderly individuals, to identify initial phases of subsequent cognitive deterioration. In a recent study (Deiber et al., 2015), participants were evaluated with an extensive neuropsychological battery (Giannakopoulos et al., 2009): those with a CDR score of 0.5 but no dementia and a score more than 1.5 standard deviations below the age-appropriate mean in any of the neuropsychological tests were confirmed to have MCI. Eighteen months after the baseline evaluation, only control subjects underwent cognitive reassessment with the same neuropsychological battery. Participants were placed in the deteriorated controls (dCON) group at follow-up if they had a performance of 0.5 standard deviation lower than that at inclusion for two or more neuropsychological tests. The final sample included 55 individuals in the stable controls (sCON) group, 42 in the dCON group, and 45 in the MCI group. Continuous EEG was recorded during a simple attentional and a 2-back working memory task (Deiber et al., 2009). The Laplacian-transformed EEG signal was segmented into epochs of 5500 ms, starting 1500 ms before stimulus onset. ERPs were obtained by stimulus-locked averaging of the signal with a 200 ms pre-stimulus baseline correction. To detect and characterize the event-related EEG oscillations whose latency and frequency ranges are not known a priori, a time-frequency (TF) analysis based on a continuous wavelet transformation of the signal was applied (complex Morlet's wavelets). Analysis was performed in the θ, α and β frequency bands. Inter-trial coherence (ITC) is a time-frequency domain measure of event-related phase locking across trials, also referred to as phase-locking factor. ITC values range from 0 to 1, with higher values indicating higher coherence of the phase of oscillations across trials. ITC analysis was performed in the θ (4–7 Hz), α (8–13 Hz) and β (14–25 Hz) frequency bands (see Deiber et al., 2015).

ERSP (Event-related spectral power) and ITC (inter-trial coherence) were separately analyzed within the θ, α and β frequency bands over the 9 most posterior electrode sites where their amplitude was maximal. In both tasks, stimulus presentation elicited a transient increase of θ power (ERS) followed by a decrease of α and β power (ERD). An increased α and β ERD as well as decreased β ITC during the successful performance of simple attention and working memory tasks are associated with the subsequent development of neuropsychological deficits in healthy elderly controls. In the α range, the posterior ERD was enlarged in dCON and MCI as compared to sCON, suggesting an increased mobilization of resources engaged for attention and working memory in these groups. In the presence of preserved task performances, such increases were usually interpreted as compensatory phenomena related to the necessity to enhance the activation of the memory networks in order to guarantee accurate task achievement. Alternatively, the increased activation could represent an early sign of loss in brain efficiency. Modulations in the β range were less obvious than in α range. The β ERD was of higher amplitude in dCON than sCON and MCI, but did not differ between sCON and MCI. This parameter (decrease of β activity) is determined by exogenous, bottom up factors (Engel and Fries, 2010). Consistent with this idea, the increase of β ERD in dCON as compared to sCON can reflect an enhancement of attentional recruitment devoted to stimulus processing.

Inter-trial coherence is particularly sensitive to cognitive decline in the β frequency range during working memory activation, since this index was able to differentiate two cognitive levels within the control group, in contrast to θ and α phase-locking indices. Fine-tuning regulation within higher β frequency ranges, shown to relate to attentive behavior, would be affected in the very early phases of cognitive decline (Wrobel et al., 2007).

### 6.5. Non-linear EEG analysis

The non-linear behavior of the brain activity and its reflection in electrophysiological recordings such as the EEG has attracted substantial attention since the early 80′s (Jeong, 2004; Stam, 2005; Hornero et al., 2009). The reasons were twofold. Firstly, the emergence of methods based on Chaos Theory and their promise to achieve a deterministic characterization of complex time series (Grassberger and Procaccia, 1983; Wolf et al., 1985). Second, the fact that multiple neural processes are governed by non-linear phenomena and such non-linear dynamics are essential for healthy, adaptive cortical activity, up to the point that abnormal non-linear dynamics has been related to a number of brain diseases (Breakspear, 2017).

The early application of non-linear methods based on Chaos Theory to spontaneous EEG activity in AD showed lower correlation dimension (D2) (Grassberger and Procaccia, 1983) and largest Lyapunov exponent (L1) (Wolf et al., 1985) values than control subjects (Jeong, 2004). These findings were interpreted as a reduction in number of variables needed to describe the dynamics of the EEG (D2) and a loss of flexibility in information processing (L1). This is because D2 is a measure of the geometry of the attractor that describes the EEG signals whereas L1 accounted for how much similar activity diverged over time (Jeong, 2004). Despite their different focus on static and dynamic properties of the EEGs, the results of both D2 and L1 were associated with a reduction of complexity in EEG activity due to AD (Jeong, 2004). Such interpretation of AD as a disease affecting the complexity of EEG signals is still valid today (Garn et al., 2015; Smits et al., 2016; Azami et al., 2017a).

Nonetheless, the application of approaches based on Chaos Theory, such as D2 and L1, to EEG activity was quickly dismissed due to major methodological issues. This led to a re-examination of the field, which resulted into two alternative, yet probably more profound, research directions (Stam, 2005):

(i) The characterization and modelling of non-linear dynamics in general, in contrast to only chaos.
(ii) The development of novel non-linear measures more suitable for application to noisy and multivariate recordings such as the EEG.

Methods of non-linear EEG analysis can be categorized into three main groups:

- Fractal dimension metrics, including Katz and Higuchi's definitions (Higuchi, 1988; Katz, 1988).
- Irregularity estimators, including sample entropy (Richman and Moorman, 2000) and permutation entropy (Bandt and Pompe, 2002).
- Multiscale metrics (Humeau-Heurtier, 2015), including multiscale sample entropy (Costa et al., 2005) and derived approaches such as multiscale dispersion entropy (Azami et al., 2017a).

The concept of fractal dimension refers to a non-integer dimension of a geometric object. Hence, metrics such as Katz and Higuchi's fractal dimension are conceptually related to D2. However, a crucial difference with D2 is that these fractal dimensions are computed in the time domain rather than requiring the reconstruction of the signal attractor, thus making them faster (Esteller et al., 2011). These metrics have been applied to spontaneous EEG activity in AD showing that patients had reduced fractal dimension compared to healthy controls (Henderson et al., 2006), especially in temporal-occipital regions (Smits et al., 2016).

A prolific and powerful framework for the non-linear characterization of EEG activity is that of information theory and entropy measures. In this context, metrics such as sample entropy (SampEn) can be seen as conditional entropy estimators as measures of the rate of production of information within a signal (how much information previous samples of the time series provide about the future points) that indicate its level of predictability (Faes et al., 2015). Entropy metrics have been used to analyze spontaneous EEGs in AD and in MCI. The results showed reduced irregularity in AD patients' EEG activity. Nonetheless, these results must be taken with caution due to the reduced size of the sample used in a number of those publications and the fact that the ability to distinguish between patients and controls may depend on the values of the parameters used in the non-linear metrics (Simons et al., 2018).

The third major category of non-linear measures are those related to the multiscale behavior of signals and the concept of complexity, which is here understood as sophisticated behavior beyond that of both fully predictable and deterministic systems and that of merely random oscillations (Costa et al., 2005; Yang and Tsai, 2013). Thus, completely ordered (i.e., predictable) or random systems are not physiologically complex (Goldberger et al., 2002). A working measure of complexity was proposed by quantifying entropy (originally SampEn) over multiple temporal scales obtained from "coarse-grained" versions of the signals under analysis (Humeau-Heurtier, 2015; Azami and Escudero, 2018a, 2018b). This method was called multiscale (sample) entropy (MSE) (Costa et al., 2005) and it has inspired the application of entropy metrics in a multiscale way (Humeau-Heurtier, 2015; Azami et al., 2017a).

MSE has been applied to reveal significant differences at a range of temporal scales between the EEG activity of patients with AD and controls (Escudero et al., 2006; Yang et al., 2013; Coronel et al., 2017). The results indicate that the spontaneous EEG activity of AD patients is less complex than that of controls at short temporal scales (associated with higher frequencies) but this tendency reverses at longer temporal scales (related to lower frequencies) where the AD patients seem to have higher complexity (Escudero et al., 2006; Yang et al., 2013). Similar results have been obtained with multiscale dispersion entropy (MDE) (Azami et al., 2017b). This finding poses intriguing questions about the dependency of the complexity of brain activity on the temporal scales and frequency range under analysis. These issues have begun to be investigated recently (Courtiol et al., 2016; Azami et al., 2017b) but further research is needed to obtain a comprehensive interpretation of the application of multiscale methods to EEG signals and their relationship with other brain activity such as connectivity (Stam, 2005). This could be complemented with the use of appropriate computational models of EEG activity that would allow the inspection of the dependencies between structural and functional connectivity, diverse non-linear estimators and biophysical parameters (Escudero et al., 2015; Ibanez-Molina et al., 2019).

Arguably, one of the limitations of the non-linear methods surveyed so far is that they are applicable to single (univariate) signals only. Multivariate versions have become recently available (Ahmed and Mandic, 2011; Labate et al., 2013; Azami et al., 2017a; Azami and Escudero, 2017; Deng et al., 2017) but their use to inspect EEG activity is still in its infancy.

Finally, it is worth mentioning that most results come from spontaneous recordings but the recent availability of methods applicable to short time series enable the non-linear analysis of EEG activity recorded during tasks (Morison et al., 2013; Garn et al., 2015; Timothy et al., 2017), something that could result in increased sensitivity and/or specificity to early AD.

### 6.6. Graph theory application and brain connectivity methods

Time series of cortical electric neuronal activity can be used for estimating cortical connectivity, based on a relatively simple concept in which the 'two places' could be replaced by 'two neuronal assemblies': "*Two places are functionally connected if their activity time series are similar*" (Worsley et al., 2005). However, from a formal point of view, there are many different ways to define similarity between signals including those from EEG.

Such methods are mainly based on the exact low resolution electromagnetic tomography eLORETA (Pascual-Marqui et al., 2011) an algorithm representing a linear inverse solution for EEG signals that has no localization error to point sources under ideal (noise-free) conditions (Pascual-Marqui, 2002). In order to obtain connectivity values a Lagged Linear Coherence algorithm is applied as a measure of functional physiological connectivity (Pascual-Marqui, 2007a, 2007b). Moving from the scalp-recorded EEG potentials distribution, the cortical 3-D mapping of current density (source localization) is carried out via eLORETA as detailed in previous studies also providing the proof of its exact zero-error localization property (see Pascual-Marqui, 2007b, 2009).

Several recent publications from independent groups (Canuet et al., 2011; Barry et al., 2014; Aoki et al., 2015; Ikeda et al., 2015; Ramyead et al., 2015; Vecchio et al., 2014b, 2014c, 2015, 2016b) supported the idea of a correct source localization using eLORETA; such idea remains true not only with high-density EEG recordings, but also with the standard 20-channel EEG montage (10–20 system).

Connectivity can be computed by eLORETA software in the regions of interest (ROIs) defined according standardized Brodmann areas for left and right hemispheres in individual cases (Talairach and Tournoux, 1988). Intracortical Lagged Linear Coherence obtained via the "all nearest voxels" or those in a sphere of 19 mm radius methods and selected on the basis of the number of considered nodes (Pascual-Marqui, 2007a; Pascual-Marqui et al., 2011), can be individually computed between all possible pairs of ROIs for each of EEG frequency bands (Kubicki et al., 1979; Niedermeyer and da Silva, 2005): δ, alpha 1, alpha 2, beta 1, beta 2, and gamma. Then, eLORETA current density time series

of each Brodmann area is used to estimate the functional connectivity. The Lagged Linear Coherence (LagR) algorithm implemented in eLORETA is used to obtain functional physiological connectivity not affected by volume conduction and low spatial resolution (Pascual-Marqui, 2007a).

Network analysis requires that the original empirical data (in our case the EEG signals) are converted in a graph (weighted or unweighted, directed or undirected) first by defining what should be considered a node, and what can be considered a link (Stam, 2014). Core measures of graph theory can be computed with http://www.brain-connectivity-toolbox.net (Vecchio et al., 2014b; Miraglia et al., 2015, 2016), which defined two of the main brain properties: segregation and integration. Segregation is defined as the degree to which network elements form separate clusters and their complex can be defined as clustering coefficient (C) (Rubinov and Sporns 2010); integration refers to the level and amount of network interconnection favoring exchange of information (Sporns, 2013), and it is summarized by the characteristic path length (L) coefficient (Rubinov and Sporns, 2010).

The mean clustering coefficient is computed for all nodes of the graph and then averaged (Onnela et al., 2005; Rubinov and Sporns, 2010) describing the tendency of network elements to form local clusters (de Haan W et al., 2009). Starting by the definition of L (Onnela et al., 2005; Rubinov and Sporns, 2010), weighted characteristic path length $L^w$ (Onnela et al., 2005; Rubinov and Sporns, 2010) represents the shortest weighted path length connecting two nodes.

Small-worldness (SW) represents the ratio between normalized C and L - $C^w$ and $L^w$- with respect to the EEG frequency bands. For example, to obtain individual normalized measures characteristic path length and clustering coefficient were divided by the mean obtained by the average of each measured parameter in all EEG frequency bands for individual subjects (Vecchio et al., 2018). Data normalization with respect to surrogate networks could not be done due to the weighted values of the considered networks. How does the "graph theoretical" model compete with other types of EEG analysis methods and how does it contribute to AD diagnosis? To the same EEG epochs utilized for graph valuation this type of classifier was compared to other kinds of methods of EEG analysis currently used for AD studies, namely spectral coherence and power spectrum; such methods showed 51.79% sensitivity, 100% specificity and 68.86% accuracy. These results are promising but less significant than the one from small world analysis (Vecchio et al., 2018).

Currently, network science is developing along a sophistication of network measures and models, introducing new concepts, such as cost-efficiency, hierarchical modularity, vulnerability to random or targeted attack, and the notion of rich clubs.

Transitivity (Tw) is another graph parameter: is measured as the fraction of the node's neighbors that are also neighbors of each other (Watts and Strogatz, 1998) and reflects, on average, the prevalence of clustered connectivity around individual nodes, a measure of segregation based on the number of triangles in the network. It is computed as Tw and represents a variant of Clustering Coefficient not affected by individual node normalization (Newman, 2003). More sophisticated methods describing segregation besides the presence of densely interconnected groups of regions also reflects their composition named the network's modular structure (community structure). It reflects the decomposition of network into groups of nodes, with the maximal content of within-group links (within network connections are dense), and the minimal level of between-group links (between network connections are sparse). The degree to which the network may be subdivided into such clearly delineated and non-overlapping groups is quantified by a single statistic, the Modularity (Qw). Unlike most other network measures, the optimal modular structure for a given network is typically estimated with optimization algorithms. Finally, Local efficiency ($E^w_{loc}$) is an index of the information transfer efficiency limited to neighboring nodes (i.e., nodes with direct edges to the node of interest), and indicates how mutually interlinked neighboring nodes are (Latora and Marchiori, 2001).

Within network hierarchical organization studies as obtained by the analysis of simultaneous EEG oscillations of different frequencies and cross-frequency couplings during a given task-performance has opened new research avenues into cognitive mechanisms (Buzsaki and Draghun, 2004). In fact, time modulation of the connectivity pattern of the nodes in a task-related network explains most of the performance variability -i.e. from "excellent" to "poor"- in apparently stable conditions (Ferreri et al., 2014; Vecchio et al., 2014a, 2016b). In other words, the task-performance level and the task-related choice/behavior contents are largely written in the immediate architecture of the EEG networks' connectivity, preceding the task (by a few seconds, usually).

Each EEG rhythm reflects different mechanisms and a complete view – in time, space, and frequency domains – is needed to obtain a comprehensive analysis of its functional dynamics. It is worth mentioning that, depending upon the frequency content of the examined rhythm, the time discrimination of the activation within the network frame can be as short as few msec (down to 10 msec in the high $\gamma$ band). Because of this, EEG connectivity analysis facilitates an evaluation of the time hierarchy governing the serial/parallel activation of the nodes and their time/space relationship within a given network (i.e. whether A is active before, after, or in parallel to B).

Within this theoretical frame, it is not surprising that aging processes significantly modulate the network configuration of brain connectivity. Resting-state EEG characteristics are known to change across physiological aging, with gradual modifications in spectral power profile indicating a decrease of $\alpha$ (8–13 Hz) and a global "slowing" of the background EEG, with an increase together with topographic modifications of the slower $\delta$ (2–4 Hz) and $\theta$ (4–8 Hz) rhythms (Dujardin et al., 1994, 1995; Klass and Brenner, 1995; Klimesch, 1999; Rossini et al., 2006). Changes in the posterior $\alpha$ rhythms are possibly due to the progressive degradation of the activity of dominant oscillatory thalamo-cortical circuits in the resting, awake, adult brain (Steriade, 1998; Brunia, 1999; Pfurtscheller and Lopez da Silva, 1999). Brain aging also affect the ability to time-varying synchronization of rhythmic oscillations in a network organization (Vecchio et al., 2017).

Dementias – particularly in the very early stages – mainly affect synaptic transmission and therefore represent "disconnection syndromes" (Rossini et al., 2006; Dauwels et al., 2010b; Babiloni et al., 2011a,b; Vecchio et al., 2015, 2017). However, advanced EEG analysis had limited application in early AD diagnosis; for instance a combined use of graph theory to explore brain connectivity from EEG signals and ApoE genotyping as a genetic risk factor for early interception of the *MCI prodromal-to-AD* condition have been attempted only very recently with encouraging results (Vecchio et al., 2018).

Age-related topographical changes of brain networks have been recently investigated with different modalities including diffusion tensor imaging MRI, EEG/MEG and fMRI (see reviews by Xie and He, 2011; Tijms et al., 2013; Rossini et al., 2019a). It is worth mentioning that fMRI and EEG connectivity do not reflect exactly the same physiological phenomena; in fact, transient locking/unlocking of neuronal firing as reflected by EEG phase synchronization does not require any energy consumption modification and does not produce any BOLD signal visible in fMRI.

In a global view, due to the decreased local and global connectivity parameters, the large-scale functional brain network

organization in AD deviates from the optimal small-world towards a more "ordered" architecture with a less efficient information exchange across brain areas and in line with the "disconnection" hypothesis (D'Amelio and Rossini, 2012). On the clinical ground, it is of interest the study of conditions as *MCI prodromal-to-AD*. A statistically significant difference in the SW organization was found between MCI subjects who will progress to AD (Converted MCI, particularly those who can be defined rapid converters – i.e. 1–2 years –) and MCI subjects who will not progress to AD (Stable MCI). Indeed, Converted MCI showed an abnormal increase in graph parameters for the low α rhythm, along with a decrease for the δ and γ rhythms, if compared with Stable MCI (Vecchio et al., 2018). The Converted MCI subjects also showed SW characteristics very similar to those encountered in AD patients 1 to 2 years before their conversion (Time 0 of the study, Vecchio et al., 2018). Such findings might be interpreted in light of the background physiology of α rhythm, usually defined as the "idling rhythms" of the adult brain (Niedermeyer and da Silva, 2005). Several studies converge on the idea that α is a deterministic chaotic signal involved in several functions – besides others (Stam et al., 1999) – ranging from memory formation to sensory-motor processing (Schurmann and Basar, 2001). Indeed, event-related activity studies in the healthy have shown a positive correlation between α frequency and the speed of information processing, as well as a good cognitive performance (Klimesch, 1999). Differently from α rhythms, which are widely recordable and dominate in the posterior brain areas, δ rhythms are poorly represented, thus reflecting a condition of likely α-δ "reciprocal inhibition" (Rossini et al., 2006). Furthermore, it is well known that the anatomical or functional disconnection of lesioned cortical areas generates spontaneous slow oscillations in the δ range in virtually all recorded neurons. In particular, the SW decrease in δ band represents an increase of functional inhibition and, vice versa, the opposite holds true for α band. A SW decrease in the γ band in the Converted MCI is in line with previous evidence (Vecchio et al., 2014c), showing a decrease of SW γ band in AD with respect to MCI and control subjects. The γ band (>30 Hz) mediates information transfer between cortical and hippocampal structures for memory formation (Vinck et al., 2013), particularly through feedforward mechanisms (Abeles, 1991) and coherent phase-coupling between oscillations recorded simultaneously from different neuronal structures (Fries, 2005). Both animal and human studies provide evidence that γ oscillations play a fundamental role in memory tasks. γ rhythms are involved in numerous cognitive functions, including visual object processing, attention and memory (Tallon-Baudry et al., 1998) and are strictly reflecting behavioral performance (accuracy and reaction time) in several memory tasks, including episodic memory, encoding and retrieval (Kaiser et al., 2008). Further, microelectrode intraneural recordings demonstrated that γ oscillations are pivotal in spike phase synchronization, which is at the base of EEG connectivity mechanisms (Nikolic et al., 2013).

It is worth mentioning that in a population of 145 MCI subjects followed up for 2 years, the ROC curve derived from graph-theory EEG analysis showed SW characteristics with a > 60% sensitivity (AUC 0.64, indicating moderate classification accuracy) for classifying the MCI state as a prodromal of AD (Vecchio et al., 2018). These findings are in line with previous studies (de Haan et al., 2012b; Vecchio et al., 2014c; Miraglia et al., 2016) in which SW characteristics were decreased in low frequency bands in patients with AD compared to MCI (Vecchio et al., 2018). That is, the MCI connectivity pattern was less random than that of the AD group. Moreover, significant differences between healthy elderly, MCI subjects and AD patients have been demonstrated by showing that physiological brain aging presents greater specialization (though lower values) of SW characteristics that are higher than normal in low EEG frequencies and lower in α bands (Vecchio et al., 2016a). Finally, the control analysis, with respect to AD patients, showed that Converted aMCI presented a graph theory pattern practically identical to the AD one. These findings suggest that EEG connectivity analysis, combined with neuropsychological evaluation in MCI, could be of great help in early *MCI prodromal-to-AD* identification as a first-line screening method to intercept those subjects with a high risk for rapid progression to AD.

It is of paramount interest to consider that the ROC curves gathered by a combined phenotype and genotype characteristics analysis (obtained at a low cost with widely available ApoE technology), the accuracy increased to 91.78 % (AUC 0.97, indicating a nearly optimal classification accuracy) for classifying the MCI state as a prodromal of AD (Vecchio et al., 2018). This result is in line with the fact that the ε4 allele of the APOE gene is the major risk genetic factor for pathogenesis of late-onset AD (Huang and Mucke, 2012; Giri et al., 2016).

The neurodegenerative process begins many years before the clinical symptoms with a selective attack to synaptic transmission and to the efficacy of brain dynamic connections (D'Amelio and Rossini, 2012). A plastic reorganization of the surviving neuronal circuitries – the neural "reserve" – contrasts and resists to such an attack nulling or limiting the impact on daily living abilities: this could explain the prolonged pre-symptomatic period (Rossini et al., 2006; D'Amelio and Rossini, 2012; Ferreri et al., 2003). In MCI subjects, the SW characteristics provided reliable predictions of MCI to AD progression within a relatively short time-frame. Moreover, rapid progression from MCI to AD heralds an aggressive type of dementia with a rapid degradation of daily life skills.

## 7. Toward automated EEG-based AD diagnosis?

AD diagnostic accuracy rate by experienced clinicians varies from 80 to 90% and requires a huge amount of resources, from high-tech equipment to highly trained experts that are primarily found only at medical centers in developed countries (Sarazin et al., 2012).

Consequently, non-invasive, low-cost and straightforward automated techniques for early AD diagnosis should be developed and improved. A promising candidate to achieve this goal is neural signal analysis through quantitative electroencephalography (qEEG).

Notwithstanding, in order to develop a fully automated system to support clinicians in AD diagnosis, further improvements in qEEG algorithms are required regarding artifact removal techniques, feature extraction, feature selection and automatic classification strategies. The schematics of an ideal automated EEG-based system for early diagnosis of AD (leave-one-subject-out training paradigm) is depicted in Fig. 3 (Cassani et al., 2014). A comprehensive review on the state-of-the art algorithms related to all the system components is beyond the purpose of this review: herein we will just provide some general notions about feature analysis procedures. So far the great majority of studies in EEG-based biomarkers for AD early diagnosis rely on the resting-awake experimental protocol, thus for the sake of compactness we will restrict our information to this approach. As previously described, four main effects on EEG signals from AD patients have been recurrently observed: slowing, reduced complexity, decreased synchrony, loss of frequency-dependent connectivity and neuromodulatory deficit in EEG rhythms. For the former three effects, a comprehensively review was already performed (Dauwels et al., 2010a), while for connectivity analysis the Reader is referred to the related section of this manuscript. Regarding the quantification of the neuromodulatory activity, amplitude modulation analysis was propositioned as a spectral-temporal technique, allowing direct characterization

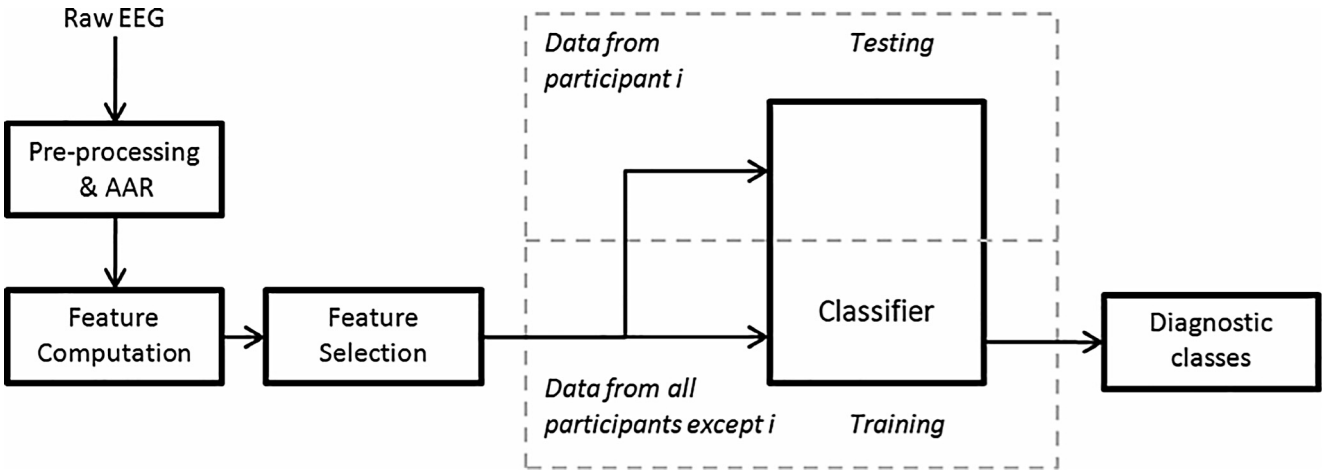


**Fig. 3.** Scheme of an automated electroencephalography (EEG)-based Alzheimer's Disease (AD) diagnosis system in the cross-validation leave-one-subject-out paradigm (Cassani et al., 2014). AAR: automated artifact removal.

of cross-frequency interaction effects by measuring the rates at which EEG bands are modulated (Falk et al., 2012; Fraga et al., 2013). The procedure of feature averaging is an interesting additional tool proven to improve the accuracy in AD diagnosis (Fraga et al., 2013). This processing stage is analogous to the epoch averaging customarily performed in event-related potential studies, but the main difference is that such averaging is done in the (non-linear) feature domain rather than in the time domain.

The combination of all the first-mentioned feature extraction techniques results in a wide-ranging collection of features. For this reason, a feature selection process necessarily should be done in an automated or at least in a semi-automated way. A large number of machine learning algorithms can be used to accomplish this task. A widely used procedure for both feature selection and classification in diagnosing AD applications is support vector machine (SVM), which achieved up to 98% accuracy in early AD detection (Falk et al., 2012; Fraga et al., 2013; Trambaiolli et al., 2011). One of the major advantages of SVM is that, using it together with the L1-norm as penalization, it leads to sparse weight vectors and allows feature selection and classification to be accomplished in the same step (Cassani et al., 2017). An interesting variation of SVM is the Relevance Vector Machine (RVM), which replaces the binary SVM classifier with a soft-decision method based on a probabilistic Bayesian learning framework and outperformed SVM when tested in a fully-automated AD diagnostic system (Cassani et al., 2014).

## 8. Conclusions

In this manuscript, we attempted to report the main and relevant tools for an integrated and interdisciplinary approach to the diagnosis of AD, particularly focusing on neurophysiological techniques and on the possibility of making an early diagnosis. We moved from the concept that a safe, valid and reliable early identification of *MCI prodromal-to-AD* is essential for a systematic screening of at risk populations, especially in view of the future arrival of disease-modifying drugs (Rossini et al., 2019b).

During the meeting held in Rome in June 2017 a panel of Experts from different disciplines has discussed this problem integrating the various disciplines involved in this field (epidemiology, neuropsychology, fluid testing, genetics, neuroimaging both structural and functional, EEG/MEG). Many of them agreed to prepare a common manuscript providing a review of the strengths and weaknesses of the individual biomarkers for early diagnosis. The International Federation of Clinical Neurophysiology has supported this meeting; such an endorsement has been triggered by the "vision" that the neurophysiological methods (in particular the advanced analysis of electromagnetic brain signals) could represent a first-line screening tool particularly for their high sensitivity to synaptic function, non-invasiveness, low-cost and widespread availability. Since EEG/MEG digitized signals can be easily translated via a technological platform from recording places on the territory to expert's centers for sophisticated analysis, harmonization of the analysis methods can be and should be accomplished. Needless to say, neurophysiological methods alone cannot reach neither the required accuracy nor the diagnostic specificity (i.e. distinguish AD from other dementias or amyloid-positive from amyloid-negative AD forms), but could contribute for a first-line screening that allows for defining high-risk subjects currently investigated only with highly sophisticated/expensive (i.e. volumetric MRI, PET with radioligands) and invasive (i.e. lumbar puncture) approaches. A future and realistic target is to try to reduce the number of cases that need second- and third-line further evaluation, making the whole scenario affordable both from the organizational and financial sides. The literature review presented here indicates several approaches that are extremely promising to open a new era in EEG/MEG methods to innovative clinical applications in the field of AD early diagnosis with huge implications.

Device-producing companies are very slow in appreciating this opportunity, while researchers from the neuroscientific clinical community seem to be - once again- on the frontline.

Let us go on and try to realize this dream!

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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