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PERSPECTIVE

Early dementia diagnosis, MCI-to-dementia risk prediction, and the role of machine learning methods for feature extraction from integrated biomarkers, in particular for EEG signal analysis

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Abstract

Introduction: Dementia in its various forms represents one of the most frightening emergencies for the aging population. Cognitive decline—including Alzheimer's disease (AD) dementia—does not develop in few days; disease mechanisms act progressively for several years before clinical evidence.

Methods: A preclinical stage, characterized by measurable cognitive impairment, but not overt dementia, is represented by mild cognitive impairment (MCI), which progresses to—or, more accurately, is already in a prodromal form of—AD in about half cases; people with MCI are therefore considered the population at risk for AD deserving special attention for validating screening methods.

Results: Graph analysis tools, combined with machine learning methods, represent an interesting probe to identify the distinctive features of physiological/pathological brain aging focusing on functional connectivity networks evaluated on electroencephalographic data and neuropsychological/imaging/genetic/metabolic/cerebrospinal fluid/blood biomarkers.

Discussion: On clinical data, this innovative approach for early diagnosis might provide more insight into pathophysiological processes underlying degenerative changes, as well as toward a personalized risk evaluation for pharmacological, nonpharmacological, and rehabilitation treatments.

KEYWORDS
Alzheimer's disease, electroencephalography, graph theory, machine learning, mild cognitive impairment

1 | INTRODUCTION

Various types of dementia represent one of the most frightening emergencies for the worldwide aging population and health systems. The large majority (50% to 70% according to the main epidemiological studies) of demented patients suffer from Alzheimer's disease (AD). Indeed, AD and related dementias do not develop in few days or weeks; disease mechanisms (such as amyloid deposition, neurofibrillary tangle formation, synaptic traffic failure and synaptic pruning, brain network disconnection, and neuronal death) act progressively for

several years before the appearance of clinically evident signs. The standard National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) and the Diagnostic and Statistical Manual of Medical Disorders Fifth Edition criteria allow diagnosis when clinical signs impacting daily living abilities due to irreversible brain pathology have already developed. A preclinical/prodromal course precedes for years or decades the early symptoms; during this interval the neuronal/synaptic reserve—partially genetically determined, but strongly influenced by life experience—allows plastic brain reorganization that counteracts the progressive loss of neurons, synapses, and connections, therefore maintaining brain functions including main cognitive abilities. It is therefore arguable that in its early stage the neurodegenerative mechanisms mainly affect synaptic transmission and functional (not yet structural) brain connectivity. Several studies argue that failure of experimental disease-modifying treatments attempted so far is due to the fact they have been carried out in patients already fulfilling dementia/AD criteria, probably too late. Along this line of reasoning, one step of paramount importance is represented by mild cognitive impairment (MCI). This preclinical stage of the aging brain is characterized by a measurable (making it therefore not an arbitrary, but an objective definition) cognitive impairment but not overt dementia[1–5] with maintained daily life skills. MCI is widely represented in the aged population (7.6% in 55- to 59-year-olds; 9.5% in 60- to 69-year-olds; 14.6% in 70- to 79-year-olds; and 23.6% in those 80 years and older[6]). Women have a higher prevalence of MCI than men. Those who reside in rural areas, live alone, and have lower educational attainments have higher MCI prevalence than others. MCI reflects a preclinical stage of AD and other types of dementia in 50 to 60% of the MCI subjects; in this case the term MCI-prodromal-to-dementia is often used.[7–10] Because of this characteristic and of its widespread presence, MCI is increasingly considered the population at risk for AD deserving special attention for validating screening methods as well as early treatments—both pharmacological or nonpharmacological—and early interventions on modifiable risk-factors.

There is a growing debate concerning the most appropriate approach for an early diagnosis. In the standard conditions, clinical features (i.e., neuropsychological tests and behavior and daily living independence scales as in the ADRDA or other diagnostic criteria) are pivotal; however, many suggest the main or absolute use of biological markers targeting pathological brain parameters typical of the disease, namely amyloid/tau metabolites and neurodegeneration track (i.e., the A→T→N pathological pathway algorithm)[11].This approach is quite interesting, but is it feasible from the public health perspective? Indeed, the public health–oriented ideal approach would be to gather individual risk scores on the 3 years after the MCI first identification with very high accuracy of identification of those who are already in a prodromal-to-dementia stage (i.e., > 95%). Most studies published so far have not actually solved the problem from this view angle, namely to reach an early risk evaluation on an individual basis prompting interventions on lifestyle, medical risk factors, and pharmacological/nonpharmacological treatments to be reserved to those MCI who are already in a prodromal-to-dementia stage.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature highlighting that Dementia in its various forms represents one of the most frightening emergencies for the aging population. Cognitive decline—including Alzheimer's disease (AD) dementia—does not develop in few days; disease mechanisms act progressively for several years before clinical evidence. A preclinical stage, characterized by measurable cognitive impairment, but not overt dementia, is represented by mild cognitive impairment (MCI), which progresses to—or, more accurately, is already in a prodromal form of—AD in about half cases; people with MCI are therefore considered the population at risk for AD deserving special attention for validating screening methods.
2. **Interpretation**: Our findings led to the fact that Graph analysis tools, combined with machine learning methods, represent an interesting probe to identify the distinctive features of physiological/pathological brain aging focusing on functional connectivity networks evaluated on electroencephalographic data and neuropsychological/imaging/genetic/metabolic/cerebrospinal fluid/blood biomarkers.
3. **Future directions**: On clinical data, this innovative approach for early diagnosis might provide more insight into pathophysiological processes underlying degenerative changes, as well as toward a personalized risk evaluation for pharmacological, nonpharmacological, and rehabilitation treatments.

To date a reliable/affordable biomarker (unique or in combination) of MCI-to-AD progression is not yet available. Ideally—again from a public health perspective—a marker should be noninvasive, low-cost, and widely available. Moreover, it should be fairly specific and accurate and valid for preclinical diagnosis with high accuracy/sensitivity/specificity on individual basis and not just at a group level.

Recent evidence supports the hypothesis that an early diagnosis and prognosis of AD during prodromal stage in amnestic MCI (aMCI) subjects might be remarkably facilitated by a proper combination of multimodal instrumental assays collecting biological (genomics, metallomics, proteomics in cerebrospinal fluid [CSF] or blood samples), structural neuroimaging (i.e., structural magnetic resonance imaging [MRI]), functional neuroimaging (positron emission tomography [PET]), and neurophysiological (i.e., electroencephalography [EEG]) biomarkers. It is a matter of fact that each biomarker-related scientific community has claimed to have developed methods able to provide high-accuracy predictions; however, all the published series so far suffer from limitations from a public health approach: limited sample size;

limited follow-up duration; lack of age-, sex-, education-matched normative data and unclear pathological cut-off definition; home-made methods that are valid only in the place where they have been developed and high intercenter variability; lack of inter-rater and intrasubject variability analysis; and a non-tested reproducibility of obtained results with several parameter collections.

The main reasons for an early identification of prodromal-to-AD MCI subjects are summarized in the following points:

1. Early identification of prodromal-to-dementia/AD individuals with MCI could facilitate the demonstration of efficacy of drug treatments currently in phase II and III trials. This may depend upon the nature of the treatment. If it mainly relieves symptoms, the effect may actually be more immediate; if it modifies disease progression, it may take a longer follow-up period to show the effect;
2. Treatment aimed at slowing the progression of AD may be more effective when administered to prodromal-to-AD MCI subjects in the early course of their progression toward AD because of the presence of a still significant neural reserve;
3. Early identification could speed up presently available interventions on known risk factors for neurodegeneration (i.e., obesity, sedentary lifestyle; poorly controlled diabetes, hypercholesterolemia, cardiac diseases) and implement rehabilitative programs (i.e., cognitive training);
4. Selecting MCI individuals who are in a prodromal-to-dementia/AD condition and restricting to them administration of disease-modifying drugs could control costs and reduce risks for adverse events in subjects with no risk of developing the disease.

At present, markers for precise and early diagnosis of AD include[12] temporo-mesial atrophy in MRI, temporo-parietal hypometabolism on single photon emission computed tomography/PET-FDG (fluorodeoxyglucose), amyloid beta (Aβ) and tau titration in CSF, amyloid imaging via Pittsburgh compound B (PiB)/PET. However, this battery of exams would cost several thousands of Euros/US dollars per individual case—a burden not affordable by any of the worldwide health systems—besides being somewhat invasive and not widely available (due to the highly sophisticated technologies required) in several countries.[13–16]

Few studies have evaluated combinations of multiple markers within the same study population.[17] Furthermore, to date no large population study with appropriate follow-up has assessed and validated a machine learning analysis for feature extraction from anamnestic data and a variety of biomarkers nor of an organizational model for screening population cohorts with combinations of biomarkers for cost, distribution, and operational feasibility. These goals are the main endpoints of some ongoing projects described below that have been launched to identify a biomarker, or a set of biomarkers, able to predict with great accuracy the conversion of MCI to AD after adequate follow-up or, better, the early identification of MCI subjects who are already in a prodromal-to-dementia/AD stage. Another aim of these projects was to define an optimal organizational model on the territory, for feasible transfer of the defined diagnostic path into clinical practice, to identify patients eligible for prescription of antidementia drugs currently under experimentation. Altogether, interaction of the above problems stress the urgent need for discovering a technique or—if a single technique is not able to reach this aim—a combination of techniques for identifying MCI individuals at high risk of developing clinically evident AD or, better, who are already affected by a prodromal stage of AD. Interestingly enough, the amount of information contained by several biomarkers in combination and anamnestic data is so high and in some cases correlations are so complex that the human intelligence is not sufficient to identify and manage them in a proper way and in a time affordable for a risk-level diagnosis. An approach via machine learning methods could be very helpful.

Within this theoretical frame several initiatives have already been launched:

A. The Italian Interceptor project, which started in 2018,[18] with six different biomarkers (an extended battery of neuropsychological and clinical tests including Mini-Mental State Examination [MMSE], Delayed Free Recall and Free and Cued Selective Reminding Test [FCSRT], Clinical Dementia Rating Scale [CDR], Amsterdam Instrumental Activities of Daily Living [IADL] Questionnaire–short version, Neuropsychiatric Inventory [NPI], Rey's word list, letter fluency, category fluency, Rey's figure, Frontal Assessment Battery [FAB], Poppelreuter–Ghent overlapping figures [PGT], Raven's colored progressive matrices, Stroop test, Trail Making Test [TMT], Screening for Aphasia in Neuro Degeneration [SAND]).
B. A model of nationwide organization with biomarker-specific expert hub centers receiving specimens/images/signals from recruiting spoke centers via a technological platform is also validated.
C. A European research network which started in March 2021, using the machine learning approach to the analysis of electroencephalographic and magnetoencephalographic signals together with apolipoprotein E (*APOE*) genotyping in a cohort of 1000 MCI subjects from four recruiting centers (AI-MIND) for MCI prodromal-to-AD early identification in combination with neuropsychological tests. Of note, the mentioned data will be of public access at the end of the project.

Final results of such multicenter studies would provide useful information to select the combination of markers to be used in large populations of subjects at risk of dementia (i.e., MCI subjects). The expected results of the clinical and preclinical studies will contribute to optimizing the financial resources devoted to the instrumental assessment of MCI subjects and to better understand the neurobiological correlates of dementias including AD at early stages. The prognostic value of the whole set of baseline characteristics will be assessed following the guidelines about multivariable prognostic models.[19] Particular attention will be devoted to the statistical check of the goodness of fit (internal validity) and to the reliable quantification of the predictive accuracy (external validity).

2 | THE CONTRIBUTION OF MACHINE LEARNING METHODS

This perspective is focused just on specific aspects of recent scientific literature, but a lot of other kinds of EEG data analysis and of classification techniques currentlyavailable obtained similar (or worse but not better) results.

In recent years, modeling the human brain as a complex network has provided a powerful mathematical framework to characterize its organization while aging processes and eventual neurodegeneration deviate from the healthy brain network configuration. In the past decade, the combination of non-invasive neuroimaging techniques and graph theory (a mathematical method) enabled mapping of the human macroscopic structural and functional connectivity patterns of brain networks in vivo (i.e., connectome) and has attracted growing research applications. One of the most influential findings is that human brain networks exhibit prominent small-world (SW) organization, a concept first introduced by Watts and Strogatz;[20] such a network organization allows an optimal balance between local specialization and global integration promoting efficient information on segregation/integration mechanisms. This is mainly based on frequency- and time-dependent synchronization and phase coherence of EEG sinusoidal oscillations (which actually reflect rhythmic firing of the neuronal assemblies) at low energy costs, which presumably results from natural selection under the pressure of a cost-efficiency balance. For the duration of phase coherence, the coherent neuronal assemblies bind/unbind for information exchange with no change in energy consumption. Moreover, the SW organization undergoes continuous changes during normal brain maturation and aging and exhibits dramatic alterations in different neurological disorders including the neurodegenerative ones.[21–25]

Several kinds of classifiers based on machine learning methods have been developed in relatively recent years in both prediction of conversion to dementia[26–28] and dementia classification to distinguish AD from frontotemporal dementia and other dementias,[29–32] supporting the hypothesis that the machine learning tools could aid the differential diagnosis of dementia. One of the commonly used machine learning classifiers is named support vector machine (SVM), which identifies the features that drive classifier performance. An SVM algorithm trained on a training dataset can generate feature weights corresponding to the relative contribution of an individual feature to successful differentiation of two groups. Following this, the classifier can be applied to a separate testing dataset to assess the accuracy of the classifier in differentiating two groups of subjects/patients. We present in detail the approach for EEG analysis, but the same is replicable for any biomarker or biomarker combination (Figure 1).

As previously stated, synaptic transmission and functional brain connectivity (later in the disease course also structural) are the initial targets within a brain under neurodegenerative attack as in dementias. It is widely accepted that neurophysiological techniques, namely the EEG analysis, provide remarkable information on both parameters (synaptic transmission and functional connectivity). On this basic assumption, it is argued that EEG signal analysis for connectivity can probe quite nicely the synaptopathy characterizing early dementia stages. EEG—differently from magnetoencephalography (MEG), which requires special environments and expensive technology—is widely available, low cost, and non-invasive—three prerequisites extremely important for public health large population screening methods.

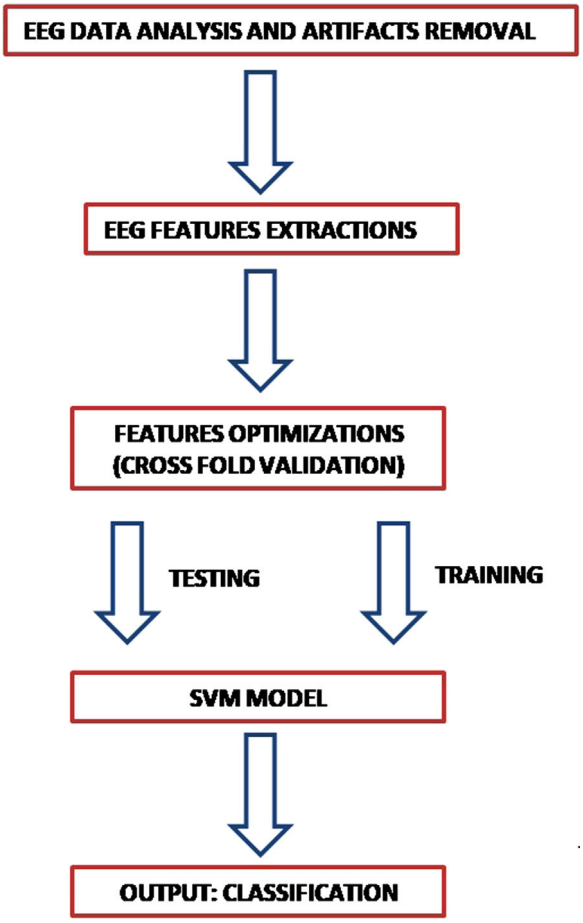

FIGURE 1 Different steps of a machine learning study of electroencephalogram (EEG) data toward the early prediction of mild cognitive impairment subjects' conversion to dementia. SVM, support vector machine

One problem to address with the SVM contribution was to estimate the AD/dementia probability given a set of EEG features, namely the data coming from SW values for delta, theta, alpha 1, alpha 2, beta 1, beta 2, and gamma EEG rhythms. The problem has been hence brought back to estimate a binary classifier, in which zero means healthy and one is AD/dementia. This approach is composed by three phases: feature standardization, feature dimensionality reduction through principal components analysis (PCA), and input classification using SVM. The aim of the first two phases is to preprocess the data and make easier the solution of the classification problem.

Standardization is a procedure to convert a random variable into a random variable with "standard" distribution, namely with zero mean and standard deviation equal to 1. The main advantage of standardization is to avoid attributes in greater numeric ranges dominating those in smaller numeric ranges. Another advantage is to avoid numerical difficulties during computation.

PCA is a dimensionality reduction technique used to map the features to a lower-dimensional space. PCA is therefore a method for reducing the dimensionality of the datasets, increasing interpretability but at the same time minimizing information loss. It does so by creating new uncorrelated variables that successively maximize variance. Finding such new variables, the principal components, reduces to solving an eigenvalue/eigenvector problem, and the new variables are defined by the dataset at hand, not a priori, hence making PCA an adaptive data analysis technique.

PCA technique operates as follow:

1. Compute covariance matrix.
2. Factorize the covariance matrix in canonical form.
3. Feature projection into the subspace composed by the eigenvector associated with the eigenvalues that describe 80% of the total variance.

The features obtained by dimensionality reduction through PCA described are used to train a binary classifier based on SVM.

The SVM is a hyperplane, or a set of hyperplanes, that can be used to classify a new input. Intuitively a good separation between classes is composed by the hyperplane with higher distance (called margin), from a point in the dataset belonging to each class, because in general the greater the margin the lower the classification error.

2.1 | Training and evaluation

The standard approach in a machine-learning environment to train and evaluate a statistical model is to randomly split the dataset into a training set and a test set. The training set is used to train the model. This means that the model sees and learns only from the data set that defines the error function minimized during training as explained in the previous section. The test set is used to evaluate model performance as represented by classification accuracy in our case.

The SVM approach has been recently applied to EEG signal analysis for healthy versus AD classification.[29] To have a complete and exhaustive model evaluation in a previous study the following cross-validation technique was used: the dataset was iteratively and randomly split into 80% training set and 20% testing set 100 times. At each iteration the model was trained making use of the training set and the accuracy being computed on the testing set. The final accuracy was computed as the average of accuracy for all the iterations. To assess variance between the different iterations the standard deviation was also obtained. A similar approach was followed to compute sensitivity, specificity, area under the curve (AUC) and receiver operating characteristic (ROC) curves. The classification process was then carried out via machine learning methods considering the seven SW values (i.e., SW index computed in delta, theta, alpha 1, alpha 2, beta 1, beta 2, gamma frequency EEG bands). It is worth mentioning that at the end of this analysis the ROC curve showed an AUC of 0.97 ± 0.03 (indicating very high classification accuracy), while the resulting classifier showed 95% ± 5% sensitivity, 96% ± 3% specificity, and 95% ± 3% accuracy for the classification of AD rwith espect to control subjects. When graph theory analysis of EEG signals is combined with *APOE* genotyping an extremely high level of accuracy in identification of AD from cognitively unimpaired elderly as well as MCI-prodromal-to-AD cases can be reached.[17]

Within the "quest" for the "best performing biomarker" one of the main "competitors" are neuroimaging methods. Seminal guidelines by Dubois et al.[33] have emphasized functional evaluation of regional cerebral blood flow/metabolism (PET-FDG) in the condition of resting state, as well as for in vivo estimation of the accumulation of amyloid proteins in the brain (PET-PiB). However, PET is partially invasive, expensive, and scarcely available especially considering the numbers of subjects fitting with MCI criteria in Western countries and the limited availability of this technology. Structural MRI markers are relatively low-cost, non-invasive, and more available than PET devices. Along this vein, it has been shown that brain atrophy as revealed by structural MRI is able to discriminate preclinical stages and time evolution of AD at 1-year follow-up.[34–36] Among these procedures with diffusion-weighted imaging (DWI) and fiber-tracking, with voxel-based morphometry (VBM), MRI with diffusion tensor imaging (DTI), fractional anisotropy (FA), and mean diffusivity (MD) are all methods enabling useful information on MCI progression.[37–39] A recent study found high levels of MD in the hippocampus, which correlated with cognitive performance scores, are not clearly pathological but falling in the lower portion of the range of normal in tests of declarative memory.[40] Volumetric analysis of temporal and parietal lobes are good predictors of transition from MCI to AD.[41] Walhovd et al.[42] showed that good accuracy of classification of stable versus converting MCI subjects is obtained by morphometric MRI measures (hippocampal volume, entorhinal, and retrosplenial cortical thickness) in logistic regression analysis. MRI measures and the total tau (t-tau)/Aβ42 ratio from CSF were predictors of diagnostic status, yielding an overall classification accuracy of 88.8% and approximately 78% explained variance. Another "competitor" for early diagnosis is examination of CSF, mainly for beta and tau metabolites. Yakushev et al.[43] aimed to compare CSF levels of t-tau, phosphorylated tau (p-tau181), and PET to (18)F-fluorodeoxyglucose (FDG-PET) in the differential diagnosis of AD under clinical conditions. In a cross-sectional, blinded, single-center study, they examined a sample of 75 unselected AD patients (n = 24), aMCI (n = 16), other dementias (n = 13), and nondemented controls (n = 22). Discriminative accuracy, sensitivity, and specificity were calculated and compared using ROC analyses. p-tau181 and FDG-PET were comparable in separating AD from controls (sensitivity: 67% vs. 79%; specificity: 91% for both) and patients with other dementias (sensitivity: 71% vs. 79%; specificity: 100% for both). The sensitivity of p-tau181 in differentiating MCI patients from controls was significantly ($P < 0.05$) superior to that of FDG-PET (75% v.s 44%) at a comparably high specificity (82% v.s 91%); t-tau measures were less accurate in all analyses.

Altogether, it is now a timely and public health-oriented strategy to define a two- or multistep (the "biomarker pyramid" for risk evaluation) process using (1) a low-cost, non-invasive, widely available, highly sensitive but not specific marker first (i.e., EEG and MRI or *APOE* genotyping) for large populations of MCI individuals to identify those with high

risk of developing dementia; (2) follow-up subjects classified with high-risk still doubtful for final diagnosis from step (1) with a specific more expensive/complex marker as Step 2 (Aβ and tau titration in CSF and blood as well as PET with amyloid/tau radioligands). Machine learning for feature extraction from a bulk of integrated and multimodal biomarker data represents a mature instrument for early identification of subjects at risk and correctly classifying them within risk levels.

3 | THE CONTRIBUTION OF ELECTROENCEPHALOGRAPHY

Computerized technology has greatly facilitated the development of novel EEG and MEG methodologies for characterizing the integrity and efficiency of the brain's functional networks. In contrast to traditional EEG and MEG methods, which typically focus only on a small subset of features in the data, the network approaches can use a wide amount of MEG/EEG data features in a single framework. For instance, a functional connection between two signals is defined by the degree of statistical dependence between the brain sources generating them. Thus, a functional connectivity network of the whole brain comprises the functional connections between all the recorded signal generator sources. In this context, because of the origin of the EEG/MEG signals from postsynaptic excitatory/inhibitory potentials, the brain network approach as measured by the time-resolved EEG and MEG methods can be considered a highly sensitive tool that has the potential to detect abnormalities in time and space, while both functional MRI (fMRI) and PET–based recordings could reveal brain connection with poorer time but better spatial resolution.

EEG markers would be ideal for the aims of the present action, as they are non-invasive, cheap, highly available, and can be easily obtained even in small community centers. Indeed web-based information and communication technology methods allow easy, fast, and low-cost transfer of digital EEG formats to high-tech centers for post-processing with dedicated software including machine learning methods. In the future, if validation studies succeed, such software can be rendered commercially available to health systems. This would constitute another by product of the ongoing projects. Indeed, modern software for EEG signal analysis can quantify on an individual basis slowing of brain EEG rhythms in AD and MCI subjects, and measure abnormalities of synchronization mechanisms of rhythmic oscillations (EEG/MEG frequency bands) of cortical pyramidal neuronal assemblies, which are at the basis of defective information transfer across brain regions[17,29,44–46] being the synaptic dysfunction leading to degradation of information transfer an early process in the neurodegenerative cascade. With respect to other techniques (such as MRI, PET) which are limited to the hospital/clinic setting, physiological measurements such as electroencephalography may play an important role as these measurements can potentially be acquired even in patients' homes. Moreover, tomographic exams could elicit claustrophobic effects, while the radio-tracers used in image collection may provoke some side effects. Moreover, with respect to other imaging techniques the EEG is intrinsically characterized by a high temporal resolution, with millisecond precision, which allows identification of brain rhythm abnormalities that can be characterized through the detection of unusual frequency patterns, generally correlated with the severity of cognitive impairment. Some limitations in the EEG application, such as the reliability associated with the electrode placement or the noise removal, could be solved providing a standardized protocol of data recording—for example, using a 10 to 20 system montage—and of data processing analysis.

Within this theoretical framework, methods assessing mechanisms of synchronization and de-synchronization of rhythmic neuronal discharges, as measured via EEG scalp recordings, have been used to assess early connectivity dysfunction.[45,47]

Several studies have showed signs of MCI and dementia in EEG signals (such as in spectral analysis of EEG rhythms and connectivity parameters) and they were used as features for classification in the machine learning environment.[48–50] Advanced EEG analysis in MCI and AD subjects has shown significant correlations with signs of neurodegeneration such as atrophy of the hippocampus[51] and impairment of the cholinergic-related transmission from basal forebrain to the cortex,[52,53] together with cognitive abnormalities. A predictive accuracy of 90% considering the basic EEG characteristics and the probability of future decline in MCI subjects has been shown.[54–57] It has been demonstrated that EEG markers can distinguish early in their clinical course prodromal-to-AD MCI subjects after about 1 year from baseline EEG recordings and clinical demonstration of MCI.[16,17,58–60]

4 | CONCLUSIONS

In conclusion, graph analysis tools for brain functional connectivity analysis combined with machine learning methods represent an interesting probe to study the distinctive features of physiological/pathological brain aging focusing on functional connectivity networks and neuropsychological/genetic/structural-metabolic imaging/CSF/blood biomarkers. Applied to patient data, this innovative approach for early diagnosis might provide more insight into the pathophysiological processes underlying age-related brain pathological changes, and toward a personalized risk evaluation for pharmacological, non-pharmacological, and rehabilitation treatments as well as for interventions on lifestyle and medical conditions that increase the risk of dementia and allow us to reserve more sophisticated and expensive technologies to the etiological diagnosis when necessary.

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CONFLICTS OF 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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