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Abstract - The utility of EEG in Alzheimer's disease (AD) research has been demonstrated over several decades in numerous studies. EEG markers have been employed successfully to investigate AD-related alterations in prodromal AD and AD dementia. Preclinical AD is a recent concept and a novel target for clinical research. This project tackles two issues: first, AD prediction at the preclinical stage, by exploiting the multimodal INSIGHT-preAD database, acquired at the Pitié-Salpetrière Hospital; second, an automatic AD diagnosis in a differential framework, by exploiting another large-scale EEG database, acquired at Charles-Foix Hospital. In this project, we will investigate AD predictors at preclinical stage, using EEG data of only subjective Memory Complainers in order to establish a cognitive profiling of elderly at-risk. We will also identify EEG markers for AD detection at early stages in a differential diagnosis context. The correlation between EEG markers and clinical biomarkers will be also assessed for a better characterization of the retrieved profiles and a better understanding on the severity of the cognitive disorder. The exploited large-scale complementary data offer the opportunity to investigate the full spectrum of the AD neuro-degeneration changes in the brain, using a big data approach and multimodal patient profiling based on resting-state EEG markers.

Keywords: clinical EEG data, Alzheimer's disease, prediction, diagnosis, cognitive profiling.

I. INTRODUCTION

Alzheimer's disease (AD) is a chronic neurodegenerative disorder that leads to progressive decline of cognitive functions, along with behavioral disturbances and insidious loss of autonomy in daily life activities. Its incidence increases exponentially with age, and doubles every 5 years after the age of 65 [1-3], being the most common cause of dementia in Western societies. As the world population ages, the frequency is expected to double by 2030 and triple by 2050 [4]. Accordingly, and because of the unprecedented level of aging in the world, the health care costs associated with AD are exceptionally high, imposing an important burden on modern societies.

The evolution of AD follows five stages. The "preclinical" stage is asymptomatic, but the brain lesions of AD are present. At this stage, the concept of Subjective Cognitive Impairment (SCI) has been proposed recently, defined by a self-experienced persistent decline in cognitive capacity in comparison with a previously normal status [5]. These subjective complaints are considered as a risk factor for AD [6,7]. Then, in "Mild Neurocognitive Disorders" (MND) stage, patients exhibit measurable memory impairments, but maintain their functional capacities [7,8]. In the "Mild AD" stage, cognitive deficits are more notable, such as memory and learning impairments. These syndromes become more severe in the "Moderate AD" stage and in the final "severe" stage of the disease, almost all cognitive and motor functions are significantly deteriorated and patients lose autonomy becoming completely dependent on caregivers. The average duration of survival of AD patients is 5-8 years after clinical diagnosis [9].

In the initial stages of the disease, AD targets limbic regions that subserve episodic memory, leading to a relatively circumscribed inability to learn and retain new information. Also, a disruption of fronto-hippocampal connections has been found to occur from the early stages of AD, in parallel with hippocampal atrophy, and it has been reported that it may specifically contribute to the initial memory impairment in AD patients [10]. Over time, AD spreads to other neocortical regions [11], affecting additional spheres of cognition, such as executive functions, attention, visuospatial abilities and language. Characteristic neuropathological findings include selective neuronal and synaptic losses [12], extracellular neuritic plaques containing the b-amyloid peptide [13] and neurofibrillary tangles composed of hyperphosphorylated forms of the tau protein [14].

No medication exists to stop or reverse the disease progression, and many therapeutics trials failed and their cost-effectiveness has been questioned [15,16]. Current major anti-AD medication trials are focusing on "preclinical" stage, in order to treat before symptoms development. Therefore, AD detection at MND and preclinical stages becomes an important issue for the scientific community.

Besides, there are currently no specific markers that can confirm the AD diagnosis with sufficient certainty, especially in the early stages. Thus, there is a crucial need for real advances to identify reliable AD markers for profiling elderly at-risk, diagnosis and monitoring disease progression.

New approaches to these complex challenges require a mix of resources and skill sets from different disciplines to enhance and forward AD research. This is the objective of our collaborative research work that we present in this paper. The project started in December 2018 and involves three French partners: two hospitals from AP-HP in France, Salpêtrière Hospital and Charles-Foix Hospital, and Samovar Laboratory of Télécom SudParis.

This paper offers an insight on current transdisciplinary research, including data analytics computing and clinical data fusion, for prognosis, diagnosis, and monitoring the evolution of AD. By relying on signal processing, data analytics and machine learning techniques, we target to identify neuro-imaging- and new neuro-dynamic biomarkers correlated with AD, which contribute to a better understanding of the brain dynamics of AD patients, and improve the prediction of elderly at-risk and the reliability of AD diagnosis.

This research project concerns the multi-dimensional profiling of elderly at-risk for AD in a differential framework, and exploits two complementary large-scale EEG databases, acquired at Salpêtrière and Charles-Foix Hospitals. Télécom SudParis team is in charge of processing and analyzing these two databases by applying signal processing methods, statistical and machine learning techniques. Such analyses will be based on the clinical expertise of the medical staff.

II. State of the art

The prognostic utility of electroencephalography (EEG) in Alzheimer's disease (AD) research has been demonstrated over several decades in numerous studies [17-27].

EEG is a non-invasive, relatively inexpensive, and potentially mobile technology with high temporal resolution (on the order of milliseconds). It was mainly investigated as a tool for AD diagnosis, by comparing EEG recordings of AD patients only to those of control subjects (healthy subjects) [28-33].

The measurable electrophysiological changes may be due to loss of gray matter and, more importantly, loss of neuronal connections [34]. EEG biomarkers have been employed successfully to investigate AD-related alterations in the brain dynamics with two main approaches - using spontaneous resting-state EEG (rsEEG) and functional EEG (fEEG) based on event-related responses (ERP). Several brainwave components of the rsEEG could be altered in various stages of AD.

Evidence from a number of studies indicates that AD leads to a reduction in the complexity of EEG signals and changes in EEG synchrony, in prodromal AD and AD dementia. These modifications in EEG recordings have been used as discriminative features for AD diagnosis. Several methods were developed for assessing the complexity of EEG signals. The correlation dimension and the first positive Lyapunov exponent were frequently used [20, 35-39]. It was found that EEG signals from AD patients exhibit lower values of such measures than signals from healthy subjects. Other information-theoretic methods, entropy-based approaches in particular, have emerged as potentially useful EEG markers of AD [21-23,25,26]: epoch-based entropy [21-23], sample entropy [24], Tsallis entropy [25], approximate entropy [40,41], multi-scale entropy [26], and Lempel-Ziv complexity [42].

Since AD is hypothesized to induce functional disconnection between brain regions, other works focused on synchrony changes detection [19-22] between pairs of EEG signals. A large variety of measures has been developed to quantify EEG synchrony: correlation coefficient [27], coherence [27,43,44], Granger causality [27,45], phase synchrony [27,46,47], state space-based synchrony [27,46,48], stochastic event synchrony [27,44,47,49,50] and mutual information [51]. All these studies reported decreased EEG synchrony in MND and AD patients compared to healthy subjects.

To discriminate AD patients from healthy subjects, all the above-mentioned studies analyzed the EEG signals either in the time domain or in specific standard frequency bands: 0.1–4Hz (delta band), 4–8Hz (theta band), 8–12Hz (alpha band), 12–30Hz (beta band) and 30–100Hz (gamma band) [39,52] or in the whole frequency range between 4 and 30Hz [27].

Spectral analysis studies reported that, in prodromal AD and AD dementia, there is an enhancement of low-frequency waves in the theta [53] and delta bands in the temporal and occipital lobes, as well as a reduction of higher-frequency beta power in the temporal and occipital regions [54-56] and a decline in alpha band (8–12 Hz) power [30,57-59]. A reduced spectral coherence between the two hemispheres was also shown between alpha and beta frequency bands [60-62]. These spectral differences were also shown to be correlated with the severity of the disease [60,63,64]. Moreover, alpha rhythms are usually distributed in the occipital area for healthy subjects; in AD patients, they increasingly move towards anterior areas as the disease progresses [58,65,66]. Early stages of AD have been associated with an increase of theta activity and/or a decrease of alpha activity. In more severe stages of Alzheimer's disease, an increase of both theta and delta activities has been observed together with a decrease of both alpha and beta activities, additionally to a reduction in the amplitude of the peak of alpha frequency band [67,68]. In all these studies, a 70%-85% correct detection rate is commonly achieved for different degrees of disease severity.

All the above-mentioned investigations have some limitations:

- *(i)* First, most works report studies conducted on small databases, of around 20 persons, containing EEG signals from only healthy subjects and AD patients (a 2-class classification problem);
- *(ii)* Second, the proposed methods in the literature tend to have a low specificity, hence poor detection of healthy subjects;
- *(iii)* Third, for all these studies, the accuracy of AD diagnosis is not evaluated in a differential diagnosis context with respect to other pathologies;
- *(iv)* Fourth, at-risk- or preclinical AD individuals have not been studied systematically due to the previous lack of clear group definitions, and challenges with subtle differences to age-matched healthy controls.

III. Main goals of the project, expected innovations

This collaborative research work differs completely from the works reported in the literature on AD detection. By contrast, this project:

- First, addresses the problem of AD prognosis/prediction at the "preclinical stage" based on the fusion of EEG markers and available clinical data. It differs from previous studies in the scientific literature both due to its study population (preclinical AD) and the data analysis techniques, based on the statistical modeling of the multidimensional EEG signal and multimodal data fusion. Previously, EEG has been used mainly as a tool for AD diagnosis, as widely demonstrated by comparing EEG signals of AD dementia patients to those of healthy subjects (a classification problem). In contrast, this project investigates early AD predictors at the preclinical stage, using complex EEG data indicators in amyloid-positive and amyloid-negative subjective memory complainers (a clustering problem). Our aim is twofold:
  - *(i)* to establish automatically a profiling of elderly at-risk of AD;
  - *(ii)* to identify the markers of progression to clinical AD in asymptomatic at-risk individuals.
- Second, it investigates EEG markers for an early automatic AD detection at MND and Mild AD stages in a differential diagnosis context. To our knowledge, automatic discrimination from EEG data between SCI, MND, and Mild AD patients was not addressed in the literature. A similar work in the literature in terms of the exploited cohort is that of Liedorp *et al.* [69], on which abnormalities in different cognitive profiles were investigated based on a visual EEG assessment. Our aim in this project is twofold:
  - *(v)* to discriminate automatically possible AD patients from patients who came to the hospital with cognitive complaint but with normal age-, gender -and education-adjusted performance on cognitive tests i.e. SCI patients (AD diagnosis);
  - *(vi)* to discriminate automatically possible AD patients from SCI patients and patients with MND or other pathologies (differential AD diagnosis).
- Third, it investigates the progression towards dementia by analyzing the evolution of EEG markers, in a transversal way, from SCI, MND to Mild AD, and also in a longitudinal way.
- Fourth, it assesses the correlation between EEG markers and clinical biomarkers for a better characterization of the cognitive profiles and a better understanding on the severity of the cognitive disorder and the AD diagnosis.

This project takes advantage of two large-scale EEG databases, acquired at two clinical centers of AP-HP: The multimodal INSIGHT-preAD database and the Charles-Foix database.

IV. Description of the two clinical EEG databases

These two unique large-scale complementary databases offer the opportunity to investigate the full spectrum of the AD neuro-degeneration changes in the brain, using a big-data approach and multimodal patient profiling with a major role for resting-state EEG markers.

A. The multimodal INSIGHT-preAD database

INSIGHT-preAD (INveStIGation of AlzHeimer's PredicTors in Subjective Memory Complainers) is an on going and mono-centric cohort study from the Salpêtrière Hospital, Paris, France, which started in 2013 [70]. The cohort includes cognitively normal individuals, over 70 years, with subjective memory complaints (SMC) but normal cognitive and memory scores according to the Mini Mental State Examination (MMSE ≥ 27), Clinical Dementia Rating (CDR = 0) and Free and Cued Selective Reminding Test (Total Recall ≥ 41).

Subjects were stratified by brain amyloid status (amyloid positive or amyloid negative) according to the uptake of 18F-Florbetapir. Demographic, cognitive, psycho-behavioral, functional, ApoE status, MRI (anatomical, diffusion, resting state-fMRI, arterial spin labeling sequences), FDG-PET imaging, EEG recordings with resting state and ERP, were performed at baseline with optional Actigraphy and CSF investigations.

All subjects participated in follow-up with neuropsychological assessment, EEG, and Actigraphy every year; blood samplings for research on biomarkers, MRI, FDG-PET and amyloid-PET scans every 2 years. The clinical staff investigated the association between amyloid status and the assessed measures at baseline and month 24, and assessed the clinical status of participants at month 30 to identify the factors associated with progression to prodromal AD.

At baseline, the database contains EEG data of 318 elderly Subjective Memory Complainers, which had a mean age of 76.03 (SD 3.47) years with a mean MMSE score of 28.67 (SD 0.96) and a high educational level (6.19 [SD 2.05] on a scale of 1-8).

EEG data were recorded using a high-density 256 channel EGI system (Electrical Geodesics Inc., USA) with a sampling rate of 250 Hz. The electrodes used are sponge-based in order to have a quick application time (10–20 min) due to the elderly population. During the recording, patients were instructed to keep awake and relaxed, with their eyes closed in a quiet room. 60 s of eyes-closed resting-state were selected for analysis.

Due to the availability of resting-state EEG (rsEEG) and other multimodal information, such as amyloid-PET SUVr measures and an extensive battery of neuropsychological tests, it is possible to analyze the neuro-dynamics profiles of individuals at-risk for AD or in the preclinical AD stage by using different advanced signal analysis methods.

B. The Charles-Foix database

This database was recorded in real clinical conditions between 2009 and 2013 at Charles-Foix Hospital (Ivry-sur-Seine, France). The EEG recordings were obtained at rest and with closed eyes using a Deltamed digital EEG acquisition system for a minimum of 20 minutes.

Scalp electrodes were placed according to the modified International 10-20 system with 11 additional electrodes in a common reference montage using a sampling rate of 256 Hz. Thirty electrodes were placed on the scalp: Fp1, Fp2, F7, F3, Fz, F4, F8, FT7, FC3, FC7, FC4, FT8, T3, C3, Cz, C4, T4, TP7, CP3, CPz, CP4, TP8, T5, P3, Pz, P4, T6, O1, Oz, O2.

The patients who complained of memory impairment were referred to the outpatient memory clinic of the Charles-Foix Hospital where they underwent a battery of tests for brain disorders, including neuropsychological test, brain imaging and blood samplings. Patients with epilepsy were excluded. Each patient was given a diagnosis at the memory clinic on the basis of the clinical, brain imaging, psychometric findings, and discussions held by a multidisciplinary medical team, using the standard diagnostic criteria: DSM-IV, NINDS, Jessen criteria for SCI, Mc Keith criteria for Lewy body dementia [5,6]. We didn’t use EEG recordings to establish the diagnosis.

In this project we will pursue our previous small-scale study [21] on a part of this database. Indeed, in [21], we used EEG data of 169 patients (mean age 75±11.2 years old, range 42-97 years old; 110 women): 22 SCI subjects, 58 MND patients, 28 AD patients (DSM IV definition), 21 patients AD “mixed”, and 40 patients suffering from other pathologies such as vascular dementia, psychosis, Lewy body dementia, and non neurodegenerative disorders (cerebral vascularitis, alcoholism…).

In this project, we will extend our study on new EEG data collected at Charles-Foix Hospital from 2013, as the first data collected between 2009 and 2013 were analyzed in our previous study [21].

The database reflects what medical practitioners are facing in reality, as opposed to databases used in the literature [20,22,23,27,39,43-47] that are prone to experimental constraints that do not match the reality on the ground.

V. Scientific content

The main research approaches for this project will be rsEEG feature extraction with signal processing techniques, unsupervised clustering methods to retrieve automatically cognitive profiles, data fusion, and supervised clustering techniques for AD diagnosis in a differential framework.

As mentioned in Section II, several EEG markers were developed in the literature for AD detection. These markers will be transposed to the framework of this project and applied as biomarkers for profiling elderly at-risk for AD in a differential framework. At each step of our experiments, several EEG markers will be evaluated, as well as available clinical data. Their fusion will be also investigated to characterize AD and elderly at-risk of AD.

This research project is organized in two parts: *(i)* AD prognostic (prediction) at the preclinical stage using the multimodal INSIGHT-preAD database; *(ii)* AD diagnosis in a differential framework, using the Charles-Foix database. Experimentally, our findings on Charles-Foix database will be exploited to address the issues tackled by INSIGHT-preAD database.

A. INSIGHT-PreAD study: AD prognostic / prediction at the preclinical stage

Preclinical AD is a relatively recent concept and a novel target for clinical research, especially in the field of EEG. Due to the availability of rsEEG and other multimodal information in the INSIGHT-preAD study, it is possible to study in detail the neurodynamics profiles of individuals at risk for AD or in the preclinical AD stage by using different advanced signal analysis methods.

This study was recently approved by the scientific committee of the Salpêtrière hospital. In this project, we aim to implement and investigate this concept using large-scale rsEEG feature extraction and fusion, in order to minimize the effects of inter-subject variability and subjective signal feature pre-selection, and to maximize the effectiveness of our predictive procedure based on prognostic multi-dimensional EEG profiling.

The feature extraction involves various EEG markers whose effectiveness was already established in the literature, as synchrony measures, complexity-based measures, and non-linear measures [20-27,34-51].

In order to retrieve homogeneous subgroups from the entire available population, unsupervised clustering techniques, using multi-dimensional feature inputs, are applied. Each obtained group will be associated with a given clinical profile.

The relationship between the obtained profiles and various clinical data (brain amyloid β deposition), socio-demographic data (age, education level), and neuropsychological exam scores (FCSRT, MMSE, DMS48, Rey figure, DO80, etc) will be assessed. This will give us a new insight on the retrieved profile characterization of individuals at-risk of AD.

For our study, both eyes-closed and eyes-open rsEEG data will be used for profiling elderly at-risk for AD, due to the often complementary brain processes involved in these two resting states.

The longitudinal study, at M24 and M30, is a key point for this study in order to assess the evolution of the profiles to clinical AD and to identify the markers associated to the profiles that are at-risk for AD.

It is worth noticing that our scientific approach for AD prognostic study will be based on our expertise and findings on previous databases, especially on Charles-Foix database that contains different groups of patients: SCI, MND and AD [21]. Concerning EEG markers, we will focus on phase synchrony measure, bump modeling, parameters derived from graph theory, and Epoch-based Entropy measure that exploits a statistical modeling of the quasi-stationary and multidimensional EEG signal with Hidden Markov Models.

B. Charles-Foix study 2: AD diagnosis in a differential framework

This study was approved by the local ethical committee of Paris 6. This study will exploit the data collected between 2009 and 2013 that were analyzed in our previous small-scale study [13], and the new EEG data collected at from 2013.

In a first step, our methodology proposed in [21] will be applied on the new EEG data, in blind manner, to estimate its generalization capacity for AD diagnosis. Our proposal in [21] exploits two features: entropy-based complexity measure [21-23] and synchrony measure [71,72], both computed in different frequency ranges and for different brain regions. The most relevant measures and the most relevant frequency range were selected with the Orthogonal Forward Regression (OFR) algorithm and the random probe method [73-75] to improve the accuracy of EEG classification using a Support Vector Machine classifier (SVM) [76,77].

Our previous study didn't focus on MND; this was a drawback of our previous published work [21]. Indeed, as shown in Table 1, only 60.3% of MCI patients are well detected, and among the misclassified MND, 70% of them are considered as patients with other pathologies. Thus, we propose, in a second step, to apply other EEG markers in order to find those that characterize MND group and to evaluate the classification accuracy of each group of patients using supervised clustering techniques with probabilistic outputs. The probabilistic approach is more suitable for decision-making to experts. We will evaluate the performance of our proposal in terms of specificity and sensitivity.

In a third step, instead of assuming a homogeneous behavior of each population (SCI, MND, possible AD, and patients with other pathologies) like mostly done in the literature, we propose to exploit unsupervised clustering techniques, in a multimodal framework, on EEG markers to uncover homogeneous subgroups from all the population, some of which possibly associated with a given cognitive profile.

Table 1: Confusion matrix for AD diagnosis with 4 groups.

Groups	SCI	AD	MND	Other pathologies
SCI	81.8%	0%	18.2%	0%
AD	6.1%	89.9%	2%	2%
MND	5.2%	6.9%	60.3%	27.6%
Other pathologies	2.5%	5%	47.5%	45%

The relationship between the obtained profiles and various clinical data (MMSE, RL/RI-16) will be assessed, which will offer an insight on the severity of the cognitive disorder and the diagnosis of the disease.

Finally, the continuum of the progression towards dementia will be studied, by analyzing the evolution of EEG markers and clinical data in a transversal way from SCI, MND to AD, considering the retrieved cognitive profiles.

VI. Expected impact

This collaborative research at the regional level may facilitate further insight into largely unknown phenomena during the progression of AD neuropathology, with a focus on an integrative view of the disease, including the extension of new knowledge on the cognitive and brain compensation in its early stages.

Another expected outcome is the development of an automatic diagnostic aid-method that will provide a risk indicator for AD to the medical doctors at the preclinical stage.

Besides, the idea behind this research work is to highlight the use of EEG for AD diagnosis. This non-invasive and inexpensive technology (20 to 100 times cheaper than a brain imaging test) would offer a better patient management by allowing low-cost mass screening of AD.

This project has also an impact on health and social system. In clinical practice, AD is difficult to diagnose and discriminate from other pathologies. Misdiagnosed patients suffer from unsuitable medical care and have a societal cost. For instance, patients suffering from vascular dementia with prior AD diagnosis use substantially more medical services every year until their dementia diagnosis, resulting in incremental annual medical costs of approximately $9,500-$14,000 [78].

Our proposal of an automatic prediction method to profile elderly at-risk for AD and to detect AD at early stage will help families and caregivers to undertake the necessary actions before the onset of the disease.

These preventive actions will allow reducing financial costs for healthcare institutions, adapting care programs to each individual, and offering a better follow-up and a personalized management of patients in hospitals.

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