Diagnosis of Alzheimer's Disease using Electric Signals of the Brain
A Grand Challenge

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"I have recently been told that I am one of the millions of Americans who will be afflicted with Alzheimer's Disease..." wrote the 40th president of the United States, Ronald Reagan, diagnosed with Alzheimer's Disease (AD) at the age of 83. Presently, one American develops AD in every 68 seconds, and by 2050 the rate is expected to increase to 33 seconds [1]. AD particularly affects the elderly population. In the United States, over 10% of people over age 65 and 50% of people over age 85 are affected by AD, and its prevalence is expected to triple within the next 50 years [2]. AD causes degeneration of the nervous system, leading to loss of memory, and reduced intellectual and social skills. No known cure exists for AD, however, progress is being made in drugs that slow its progression. As AD patients are elderly, their medical treatment is complex and costly compared to other diseases. Moreover, providing medical care for the AD patients is a difficult task where the care givers undergo a large physical and emotional stress.

In the preclinical stage of AD known as mild cognitive impairment (MCI) or predementia, the symptoms are not measurable enough, often ignored, and mistaken with the normal consequences of aging. Around 6% to 25% of the people affected with MCI progress to AD every year. The two first stages of AD, known as mild and moderate AD, are characterized by symptoms such as confusion, loss of language, and long-term memory loss. These cognitive deficits are so severe that it makes the patient withdraw from the social and family life, and become more dependent. In the final stage, known as severe AD, the personality deteriorates completely and the patients become entirely dependent on their caregivers. Once diagnosed positive, the average life expectancy of the patients is less than seven years. Between years 2000 to 2008, there was an increase in deaths due to AD by 66% [1].

Diagnosis of AD, particularly early diagnosis, is important for several reasons [3]. Most of the symptoms-delaying medicines are effective when used in the early stage of the disease. Early diagnosis also allows effective treatment of psychiatric symptoms such as depression, which indirectly reduces the personal and societal costs of the disease. A positive early diagnosis gives the patients and their family the necessary time to understand the disease, to decide on the life and financial burdens of the disease, and to arrange for the future needs and care of the patients.

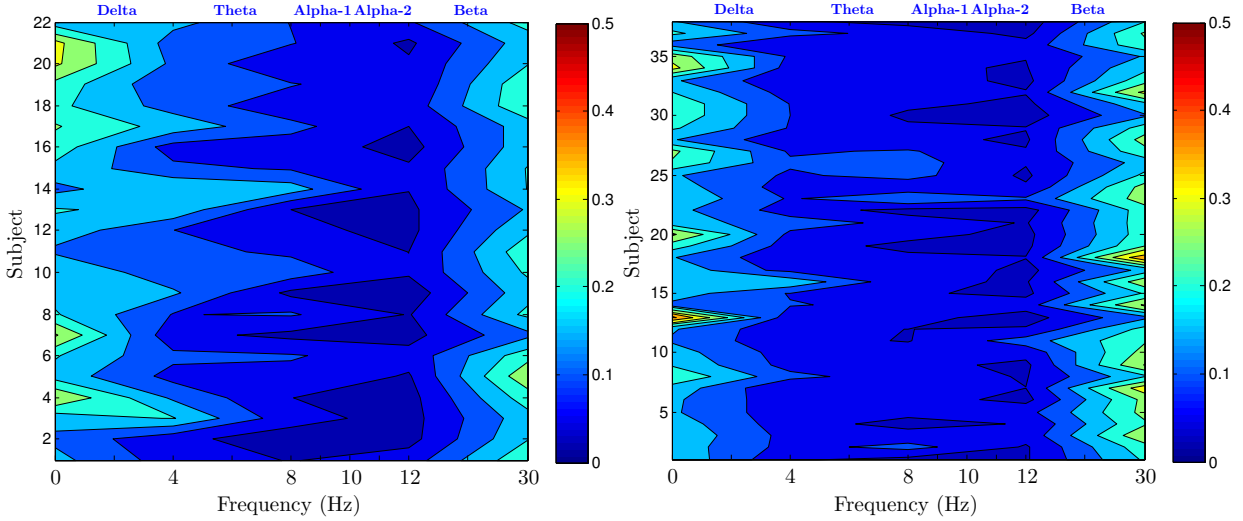
There is no specific test to diagnose AD directly, instead doctors often diagnose AD based on various tests to eliminate other possible causes [4]. These tests include simple physical and neurological examination, blood and spinal fluid tests, mental status tests, and neuropsychological tests. Increasingly, brain imaging techniques such as computerized tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) are being explored for diagnosing AD. Apart from the mental and neuropsychological examinations, other examinations are either invasive or possess radiation dose (CT/PET), and/or are costly. There is a growing demand for AD diagnosis methods that are noninvasive, fast, inexpensive, and reliable. Electroencephalography has the potential to become such diagnostic tool for AD.

We will now briefly elaborate on electroencephalography. The nerve cells, known as neurons, form the fundamental building blocks of the human brain, communicating among themselves (and other cells in the brain) by electrical and chemical signaling. The electrical signals among the neurons gives rise to an electric field on the scalp, which can be measured *noninvasively*, and this recording is referred to as electroencephalogram (EEG). EEG is considered as "window of the mind," as neurological diseases typically affect EEG in some specific ways. In recent years, many researchers have started investigating the potential use of EEG for diagnosing AD (see [3] for a review). EEG recording systems have become relatively inexpensive, compact, and mobile. Consequently, EEG can be recorded at the point of care (e.g., at home) at low cost, and hence EEG may potentially be used as a tool to screen a large population for the risk of AD. Though EEG signals often contain a wealth of information, the changes in EEG associated with AD are often not sensitive enough to show a clear differentiation, especially at early stages of AD. Significant research efforts are being made in improving the sensitivity of EEG in order to make it an effective tool for diagnosing AD.

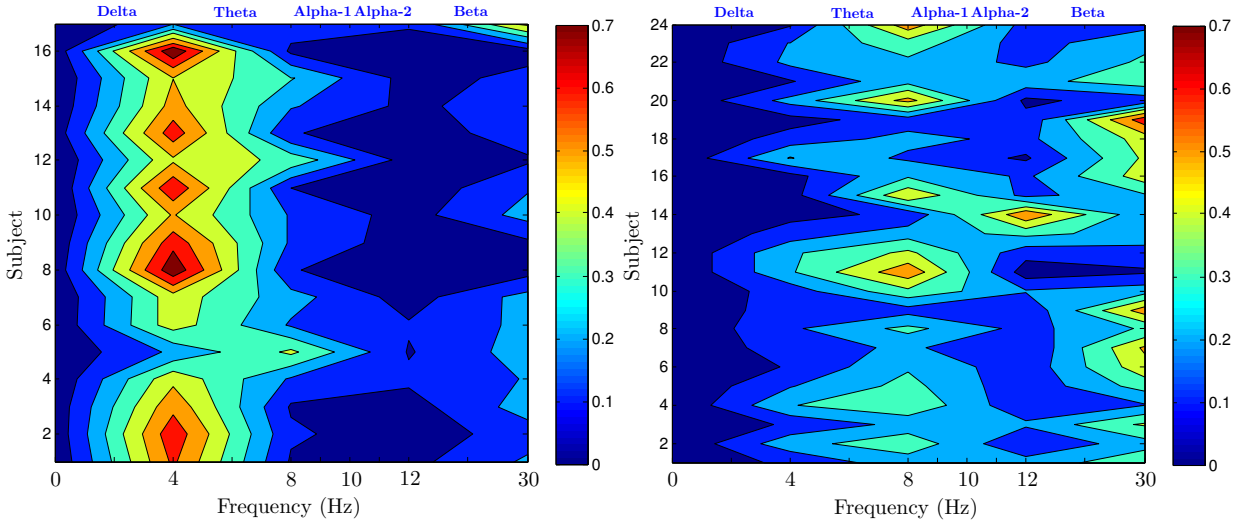
According to the literature (see [3] for a review), AD perturbs EEG in three major ways. First, the EEG of AD patients becomes *slower*, in other words, more power in the EEG spectrum is concentrated at lower frequencies. Second, AD EEG contains fewer fluctuations, and hence it is considered *less complex* compared to healthy EEG. Third, EEG signals from different regions of the brain are less correlated in AD patients

compared to healthy subjects. In the following, we briefly discuss those three characteristics of AD EEG.

Visual inspection of AD EEG show an increase in diffuse slow activity compared to EEG of age-matched healthy subjects, which is confirmed by quantitative results from the computerized spectral analysis of EEG signals. Slowing in EEG, i.e., shift in spectral power towards low frequencies, is measured by calculating relative power in various EEG frequency bands. The frequency spectrum of EEG is often divided into non-overlapping frequency bands, such as 1–4Hz (delta), 4–8Hz (theta), 8–10Hz (alpha 1), 10–12Hz (alpha 2), 12–30Hz (beta), and 30–100Hz (gamma) [5]. A slight increase of power in delta and theta band has been observed in MCI EEG (see Fig. 1(a)), and this effect is more pronounced in the case of Mild AD (see Fig. 1(b)). In addition, there is typically reduced power at higher frequency bands (alpha and beta, 8–30Hz) in both MCI and Mild AD EEG. Interestingly, the strength of perturbations in the EEG spectrum has been shown to have an intricate relationship with the degree of progress of the disease [6].



(a) MCI EEG (left) and healthy EEG (right)



(b) Mild AD EEG (left) and healthy EEG (right)

Figure 1: EEG power spectrum for (a) Mild Cognitive Impairment patients vs. control subjects; (b) Mild AD patients vs. control subjects. The effect of slowing is less visible in MCI EEG, whereas it is prominent in Mild AD EEG. (Figure reproduced from [6] under CC)

EEG signals from healthy subjects are highly stochastic and fluctuate substantially, whereas AD EEG is often more regular and less complex. EEG complexity can be quantified in various ways [6]. Information theory [7, 8] provides a variety of complexity measures, including approximate entropy, sample entropy, Tsallis entropy, and multiscale entropy. Entropy is a measure of the uncertainty associated with a random variable [7]. Some complexity measures have been developed in physics: fractal dimension, correlation dimension, and largest Lyapunov exponent. Fractal dimension is a statistical quantity that indicates how completely a fractal appears to fill space, as one zooms down to finer and finer scales. A fractal is generally

a fragmented geometric shape that can be split into parts, each of which is (at least approximately) a reduced-size copy of the whole [9]. Natural objects that approximate fractals to a degree include clouds, mountain ranges, coastlines, and snow flakes. There are several definitions of fractal dimension; correlation dimension [10] is one of them. The Lyapunov exponent of a dynamical system is a quantity that characterizes the rate of separation of infinitesimally close trajectories [11,12]. The maximal Lyapunov exponent determines the predictability of a dynamical system. A positive maximal Lyapunov exponent usually indicates that the system is chaotic.

Many of the previously mentioned complexity measures, stemming from information theory or physics, have been applied to assess the complexity of EEG. Broadly speaking, complexity measures indicate the number of distinct patterns in the EEG signals. In earlier studies and our recent analysis [3, 6], it has been observed that the complexity of MCI EEG is only slightly smaller than of healthy EEG. On the other hand, a significant loss in EEG complexity is noticed in the case of Mild AD patients, clearly indicating the progression of the disease. We conjecture that the loss of neurons and reduced anatomical and/or functional coupling among them makes the neural dynamics and hence observed EEG less complex.

An important effect of AD is the loss of interdependence among EEG signals recorded from different areas of the brain; this phenomenon may be due to the loss of coupling among the neurons. The synchrony between EEG signals can be measured in many different ways, ranging from linear (simple) measures to non-linear (complex) measures [3, 13, 14]. Probably the most basic synchrony measure is the Pearson correlation coefficient; it quantifies linear correlations between pairs of signals. The (magnitude) coherence function is an extension of the correlation coefficient from time-domain to frequency domain; it measures linear correlations in frequency domain [15]. Granger causality extends the correlation coefficient from pairs of signals to multiple signals [16]. It allows us to determine the causality of linear interactions. For instance, it is able to identify which EEG channels act as sources or as sinks. The approaches mentioned so far all focus on magnitude synchrony. Alternatively, one may investigate correlations between the phase of signals [17]. Indeed, the instantaneous phase of different signals may be strongly synchronized even if the amplitudes of those signals are statistically independent. An interesting alternative family of synchrony measures, referred to as state space based synchrony or generalized synchrony, stems from physics [18,19]. The signals at hand are assumed to be generated by some (unknown) deterministic, potentially high-dimensional, non-linear dynamical system. As a first step, one tries to reconstruct that system, by representing the signals in a state space: each signal is represented as a trajectory in that space. Signals are considered to be synchronous if their trajectories remain close to each other. A few years ago, we proposed an entirely different approach to quantify synchrony, referred to as stochastic event synchrony (SES) [20–23]; it characterizes the interaction between certain events in signals. In brain signals, those events can be spikes or transient oscillatory components.

The previously mentioned synchrony measures have been applied to AD EEG; we provide an overview in [3]. A large number of studies report a loss of EEG synchrony in MCI and AD patients. In most studies, a single synchrony measure is applied to a single EEG data set. Since almost every study considers a different measure and a different EEG data set, it is hard to compare existing studies and to verify whether results are consistent. To address this issue to some extent, we applied 35 synchrony measures to the EEG of MCI patients [14]. Most synchrony measures, especially Granger causality and SES, indicate a statistically significant loss of EEG synchrony in MCI patients compared to age-matched healthy control subjects. In an other study [24], we repeated the analysis for EEG of Mild AD patients, and observed similar loss of synchrony in those patients. Those observations are in agreement with studies by other researchers.

In summary, EEG recordings may provide us valuable information for AD screening and diagnosis. Compared to other brain imaging modalities such as MRI and CT, which visualize the brain anatomy, EEG captures the fine-grain temporal variations of brain activity, and hence seems to contain signatures of abnormal brain dynamics of AD. Specifically, the effects of AD on EEG can mainly be divided into three phenomena: slowing, reduced complexity, and loss of synchrony.

In the following, we will briefly outline some of the challenges in using EEG as diagnostic tool for AD. As EEG signals are electrical potentials, they are affected by electronic interferences and contaminated by unwanted electrical potentials. For example, EEG recordings contain external interference from power lines, artifacts due to eye blinks, head movement, and muscle activity. Various signal processing techniques are being employed to selectively remove interferences and artifacts while preserving diagnostic features. However, identifying background noise from diagnostic information is subjective, and EEG experts do not always agree about EEG artifacts and their removal [3]. Instead of removing artifacts from EEG, it is often preferable to remove the portion of EEG with artifacts and use the rest of the EEG for analysis; however, this will lead to reduction in length of EEG and may reduce sample size significantly.

More problematically, the literature on EEG of AD patients is not always directly relevant for diagnostic purposes. As discussed so far, statistically significant perturbations in AD EEG have been observed in a plethora of studies. However, that does not immediately imply that EEG can serve as a diagnostic tool for AD. For that purpose, the EEG of *individual* AD patients should significantly differ from the EEG of

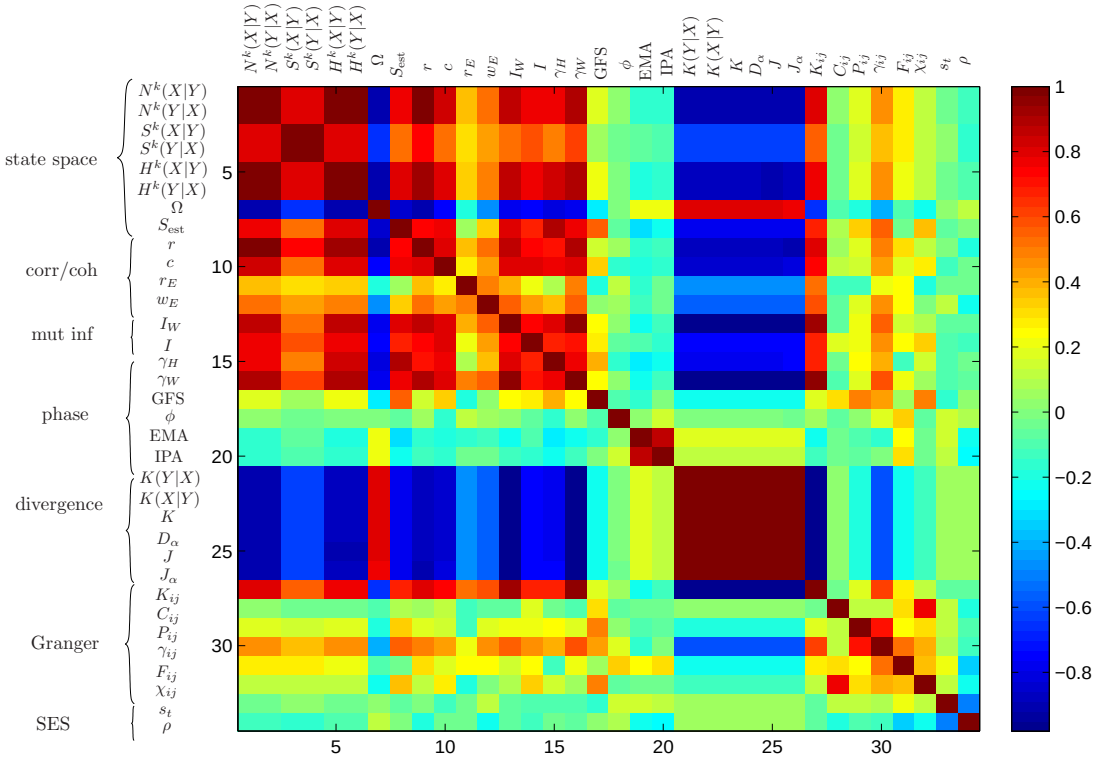


Figure 2: Correlation between the synchrony measures (red and blue indicate strong correlation and anti-correlation respectively). (Reproduced from [14] with permission)

healthy subjects and of other neurological patients. In most studies, however, effects across a population of AD patients are reported, and typically not on the level of individual patients. To address that issue, some researchers perform classification of AD and healthy EEG, where classification algorithms analyze a variety of EEG statistics, and decide in an automated fashion whether the EEG stems from an AD patient or a healthy person. As a rule of thumb, in order to be relevant for diagnosis, less than 20% of those decisions should be incorrect (classification error). It is crucial to determine reliable estimates of the classification error. In many studies on classification of AD EEG, unreliable estimates of the classification error are reported, since the classifiers are trained and tested with the same data set. As a result, the classifiers may be overfitted to the data at hand. Consequently, the reported classification results may not generalize to other data sets, and may be overoptimistic. To obtain more reliable classification results, one may for example apply crossvalidation, as has indeed been done in a handful studies (e.g., [14, 25–31]). However, crossvalidation only yields reliable classification rates if the data set is sufficiently large and the classifiers have a limited number of parameters. To obtain more reliable classification results, one should ideally use three independent data sets [3]:

- The first data set is used to train various classifiers.
- The resulting classifiers are evaluated on the second data set; one retains the classifier with the best classification results on the second data set.
- The latter classifier is then evaluated on the third data set.

The classification results on the third data set are a reliable estimate of the actual classification performance, as long as the three data sets are sufficiently large and independent. At present, unfortunately, no databases of AD EEG are publicly available. Therefore, it remains hard to assess the potential of EEG for AD diagnosis. Progress in this area is hampered due to lack of access of large and independent databases of AD EEG. In contrast, such public databases are available for ECG [32], serving as a valuable testbed for ECG researchers worldwide.

In order to distinguish AD EEG from healthy EEG, it is recommended to analyze complementary EEG statistics. In other words, we advise to compute the correlation between various EEG statistics, and to select several uncorrelated EEG statistics for classification. As a consequence, the classifiers have access to complementary information to decide whether or not the EEG at hand stems from an AD patient. For instance, in a recent study [6], we discovered strong correlation between the phenomena of slowing and loss of complexity in AD EEG. We observed significant (anti-)correlations between relative power in various

frequency bands and several complexity measures. As expected, combining relative power with complexity measures for classification of AD EEG vs. healthy EEG did not yield better results than classification based on relative power alone. On the other hand, several synchrony measures (phase synchrony, Granger causality, and stochastic event synchrony) did not seem to correlate with the relative power measures, and indeed helped to improve the classification results. Along the same lines, in our comparative study of synchrony measures [14], we observed that many synchrony measures are strongly correlated (either positively or negatively), as illustrated in Fig. 2. As a consequence, distinct families of synchrony measures may be identified. For example, from Fig. 2, it can be seen that SES is uncorrelated with all other synchrony measures, and hence it captures complementary information. This result suggests that it is not necessary to apply 35 or more synchrony measures for classification of AD vs. healthy EEG; it probably suffices to combine measures from each family.

It is also noteworthy that most of the studies on the diagnosis of AD using EEG are retrospective, i.e., they are based on the EEGs of already diagnosed subjects. So far, EEGs have not been used as a predictive tool, verified by the medical diagnosis to prove their effectiveness later. Moreover, most studies investigate how AD EEG differs from healthy EEG, whereas it also important to compare AD EEG with the EEG of other neurological patients. Another promising direction for future research is to leverage EEG with other brain imaging modalities and/or biochemical markers of AD. Although a few studies have explored such multimodal approaches, much research still needs to be done to gain further understanding in the neurophysiology of AD EEG, and its potential for AD diagnosis.

In conclusion, the EEG of AD patients has been investigated in a large spectrum of studies so far. Nevertheless, several critical bottlenecks and challenges need to be overcome before EEG can realize its potential as a noninvasive, fast, inexpensive, and reliable diagnostic tool for AD.

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