On the Early Diagnosis of Alzheimer's Disease from EEG Signals: A Mini-Review

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Abstract. In recent years, various computational approaches have been proposed to diagnose Alzheimer's disease (AD) from EEG recordings. In this paper, we review some of those approaches, and discuss their limitations and potential.

1 Introduction

Alzheimer's disease (AD) is a common neurodegenerative disorder that affects more than 10% of Americans over age 65, and nearly 50% of people older than 85; it is estimated that the prevalence of the disease will triple within the next 50 years [1]. No cure for Alzheimer's disease has been developed yet, but a number of medications are believed to delay the symptoms (and perhaps causes) of the disease. The progression of the disease can be categorized in four different stages. The first stage is known as Mild Cognitive Impairment (MCI), and corresponds to a variety of symptoms (most commonly amnesia) which do not significantly alter daily life. Between 6 and 25% of people affected with MCI progress to AD every year. The next stages of Alzheimer's disease (Mild and Moderate AD) are characterized by increasing cognitive deficits, and decreasing independence, culminating in the patient's complete dependence on caregivers and a complete deterioration of personality (Severe AD) [2].

Early diagnosis of Alzheimer's disease, and in particular diagnosis of MCI and Mild AD, is important, since medications are most effective at an early stage of the disease. Diagnosis of Alzheimer's disease is hard, however, and symptoms are often dismissed as normal consequences of aging. Diagnosis is usually performed through a combination of extensive testing and eliminations of other possible causes. Psychological tests such as Mini Mental State Examinations (MMSE), blood tests, spinal fluid, neurological examination, and increasingly, imaging techniques are used to help diagnose the disease [3].

In the last years, several research groups have started investigating the potential of electroencephalograms (EEGs) for diagnosing AD. Since EEG recording systems are inexpensive and (potentially) mobile, EEG may potentially be used as a tool to screen a large population for the risk of AD.

In this paper, we review several state-of-the-art signal processing methods to detect perturbations in EEG signals caused by AD (Section 2). We assess

the potential and limitation of such computational approaches (Section 3). At the end of the paper, we briefly address future challenges and open problems (Section 4). This paper is probably one of the few studies in recent years to provide an overview and critical assessment of various state-of-the-art signal processing methods for diagnosing AD from EEG signals.

2 Analysis of EEG of MCI and AD patients

Studies have shown that AD has (at least) three major effects on EEG (see [4] for an in-depth review): slowing of the EEG, reduced complexity of the EEG signals, and perturbations in EEG synchrony. Those effects, however, are not always easily detectable: there tends to be a large variability among AD patients. As a result, none of those phenomena allow at present to reliably diagnose AD at an early stage. Many recent studies have investigated how to improve the sensitivity of EEG for detecting AD. In the following we briefly review some of these studies; we will treat the three major effects of AD on EEG separately.

2.1 Slowing of EEG

Many studies have shown that Alzheimer's disease (AD) causes EEG signals to slow down (see, e.g., [5, 10, 18–24, 28]): AD is associated with an increase of power in low frequencies (delta and theta band, 0.5–8Hz) and a decrease of power in higher frequencies (alpha and beta, 8–30Hz, and gamma, 30–100Hz). To quantify the changes in spectral power, one has applied Fourier transforms [5, 10, 18–22, 28] and sparsified time-frequency maps ("bump models") [23, 24].

2.2 Reduced Complexity of EEG Signals

The EEG of MCI and AD patients seems to be more regular than of age-matched control subjects [6–8]. The following complexity measures have been used to quantify this reduction in EEG complexity: approximate entropy [6], auto mutual information [6], sample entropy [6, 8], multiscale entropy [6], Lempel-Ziv complexity [6], and fractal dimension [7].

2.3 Perturbations in EEG Synchrony

Numerous studies have reported decreased EEG synchrony in MCI and AD patients under resting conditions ("spontaneous EEG")(see, e.g., [19, 33, 45–58]). More precisely, the statistical dependence between spontaneous EEG signals recorded from different channels seems to be generally lower in MCI and AD patients than in age-matched control subjects. A large variety of measures have been applied to quantify this loss in statistical dependence, e.g., Pearson correlation coefficient [51], coherence [51, 52, 54], Granger causality [33, 45, 51], information-theoretic [58, 51] and state space based synchrony measures [19, 46, 51, 55, 56], phase synchrony indices [19, 51, 53, 54, 57], and stochastic event synchrony [47–51]. In a recent study, the spatial distribution of EEG phase synchrony in AD patients has been investigated [60]. By means of closely-related graph-theoretic methods, several studies have shown that EEG signals of MCI and AD patients have weaker small-world network characteristics compared to age-matched control subjects [62, 61].

The observed loss in synchrony is often attributed to a functional disconnection of the neocortex; it is probably not simply due to a loss of cortical neurons.

For example, it may result from anatomical disconnections among different cortical regions in combination with reduced cholinergic coupling between cortical neurons [58]. In particular, a common hypothesis is that basal forebrain neurons may be severely affected in AD, resulting in a cerebral cholinergic deficit that leads to memory loss and other cognitive symptoms [58].

Interestingly, in a few studies that investigate the EEG of MCI and AD patients recorded during working memory tasks, an *increase* of EEG synchrony was observed in those patients [55, 59]. This inverse effect is often interpreted as the result of a compensatory mechanism in the brain.

One should keep in mind, however, that it is hard to directly interpret results obtained with synchrony measures. The synchrony of EEG signals may be significantly affected by brain events other than changes of synchrony, and by choices (like the reference electrode) that necessary have to be made during the analysis. Furthermore, as a single active source in the brain may affect the EEG signals across the entire scalp, changes in synchrony, and especially simultaneity of some events across channels, may be observed when the activity of one source alone changes, which is remote from a change in synchrony. As an alternative, one may use inversion methods to reconstruct sources, and next apply synchrony measures to those sources. However, the inversion problem is known to be notoriously difficult, and any source reconstruction method relies on certain assumptions, which may not necessarily hold.

3 Discussion

As pointed out earlier, EEG seems an attractive brain imaging modality for diagnosing AD, since EEG recording systems are inexpensive and (potentially) mobile. Moreover, in contrast to most other non-invasive brain imaging methods, EEG has high temporal resolution, and may therefore contain crucial information about abnormal brain dynamics in AD patients.

Numerous studies have investigated the potential of EEG as a diagnostic tool for AD. At present, however, it is hard to assess whether EEG is truly useful for diagnosing AD. First of all, most studies report the results of statistical tests (p-values) without statistical post-correction. Since typically one conducts multiple tests simultaneously (sometimes hundreds or even thousands), e.g., individual pairs of electrodes or frequency bands, it is important to eliminate false positives. To this end, one may apply Bonferroni post-correction, or more powerful alternatives, such the false-discovery-rate correction method of Storey [65]. Unfortunately, not all studies on diagnosing AD from EEG signals apply such post-correction methods, and therefore, it is not always obvious how to interpret the reported results.

Second, few studies conduct discriminant analysis (linear or non-linear discriminant analysis, using support vector machines, neural networks, etc.); studies that do conduct discriminant analysis typically only report results for training data. The reported results are therefore often prone to overfitting, and they 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., [10, 8, 51]).

Third, in most existing studies, a single measure to detect EEG abnormalities 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.

Fourth, it is likely that one will need to combine various EEG characteristics in order to obtain a good diagnostic tool for AD, e.g., based on slowing, loss in EEG synchrony and complexity, and other features yet to be discovered. However, few studies systematically investigate large collections of EEG features (e.g., [10, 51]); it would be of great interest to apply dimensionality reduction methods to hundreds or even thousands of EEG features, to determine the most discriminative EEG features in a disciplined and statistically rigorous fashion. Moreover, it still needs to be verified whether the effects listed in Sections 2.1 to 2.3 are independent. For example, it may be that EEG slowing and loss of EEG complexity are two sides of the same coin.

4 Conclusions

To conclude this paper, we point out several remaining challenges and topics for future research. At present, it is fairly difficult to gain access to EEG data of MCI or AD patients. Such databases are not publicly available, in contrast to ECG and other biomedical data (e.g., [66]). As a result, it is hard to systematically benchmark and assess the existing methods for diagnosing AD from EEG signals. Moreover, virtually none of those methods incorporate biophysical knowledge about AD (but see [37]); detailed mathematical models of the pathology of AD, in conjunction with EEG data analysis, may help us to improve the diagnosis of AD. Along the same lines, one may expect further improvement by combining EEG with other imaging modalities, such as MRI (see, e.g., [31–33]), dMRI [34], TMS [35], and SPECT [36].

The correlation between AD risk factors (e.g., high plasma concentration of homocysteine [44]) and EEG characteristics needs to be investigated in greater detail. In addition, at present, the precise relation between the decline of cognition and memory and EEG abnormalities in AD patients remains largely unexplored (but see [64, 18, 17, 57]). It is also of great importance to investigate whether EEG helps to distinguish between MCI and different stages of AD (see, e.g., [16]), and between AD and other dementias (see, e.g., [25–30]).

An important degree of freedom is the EEG recording condition: one may record EEG: (i) while the subject is at rest (with open or closed eyes); (ii) while the subject performs working-memory or other tasks; (iii) while the subject is being stimulated with auditory, visual, tactile, or other signals (see, e.g., [11–15]). Depending on the recording situation, EEG signals may be more or less discriminative for MCI and AD; a systematic exploration of different recordings conditions with the aim of diagnosing MCI and AD needs to be conducted.

One may also analyze the EEG of animal models of AD (see, e.g., [63]), where the progression of AD can be rigorously assessed and controlled; such studies may enable us to relate EEG abnormalities to the neuropathology of AD. Another interesting line of research is to investigate the effect of medication and therapy on the EEG of AD patients (see, e.g., [38–43]).

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