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# A spatio-temporal wavelet-chaos methodology for EEG-based diagnosis of Alzheimer's disease

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ABSTRACT

A spatio-temporal wavelet-chaos methodology is presented for analysis of EEGs and their *delta*, *theta*, *alpha*, and *beta* sub-bands for discovering potential markers of abnormality in Alzheimer's disease (AD). The non-linear dynamics of the EEG and EEG sub-bands are quantified in the form of the correlation dimension (CD), representing system complexity, and the largest Lyapunov exponent (LLE), representing system chaoticity. The methodology is applied to two groups of EEGs: healthy subjects and AD patients. The eyes open and eyes closed conditions are investigated to evaluate the effect of visual input and attention. EEGs from different loci in the brain are investigated to discover areas of the brain responsible for or affected by changes in CD and LLE. It is found that the wavelet-chaos methodology and the sub-band analysis developed in this research accurately characterizes the non-linear dynamics of non-stationary EEG-like signals with respect to the EEG complexity and chaoticity. It is concluded that changes in the brain dynamics are not spread out equally across the spectrum of the EEG and over the entire brain, but are localized to certain frequency bands and electrode loci. New potential markers of abnormality were discovered in this research for both eyes open and closed conditions.



Alzheimer's disease (AD) is a common neurodegenerative disorder that affects about 5 million people in the United States. Currently, there is no single *in vivo* clinical test for a conclusive diagnosis of AD even in its advanced stages primarily due to overlapping symptomatology with normal aging and other dementias [17,2,3,38,28]. Researchers are focusing on finding non-invasive markers of AD in electroencephalograms (EEGs) which are clinically less cumbersome and inexpensive compared to imaging modalities. Since AD is a dysfunction of the cerebral cortex, abnormalities in cortical field potentials (recorded by EEGs) should reflect pathological changes in the structure and function of the cortex [22,6]. In this regard, *EEG slowing* [22,6,32,26,9,35] and *reduced coherence* (correlation or mutual information) [22,35,7,24,23] have been observed in AD but the evidence is not conclusive.

In the last decade, it has been hypothesized that the complexity of the human brain (directly proportionate to the information processing capability) can be represented by the *complexity* of the non-linear chaotic dynamics underlying the EEG [30,20,1,12]. Studies based on a commonly used measure of complexity in chaotic systems, the correlation dimension (CD), have claimed that the CD is increased during wakefulness and cognitive task performance [34,25,27] and is decreased due to factors that cause cognitive deficits such as sleep deprivation and epileptic seizures [11,18,4]. A similar reduction in complexity is also observed in AD, where the neuronal loss and reduction in corticocortical connectivity lead to simpler brain dynamics and impaired information assimilation by various brain regions compared to a healthy brain [31,8,21]. A related measure, *neural complexity*, has also been proposed to quantify how well the brain binds together information [37,36,33]. In neuropathologies associated with cognitive deficits, the neural complexity appears to be reduced due to a decreased capability to process information [10,16]. The largest Lyapunov exponent (LLE), a measure of EEG *chaoticity*, also appears to be reduced implying lower brain complexity in AD patients [22].

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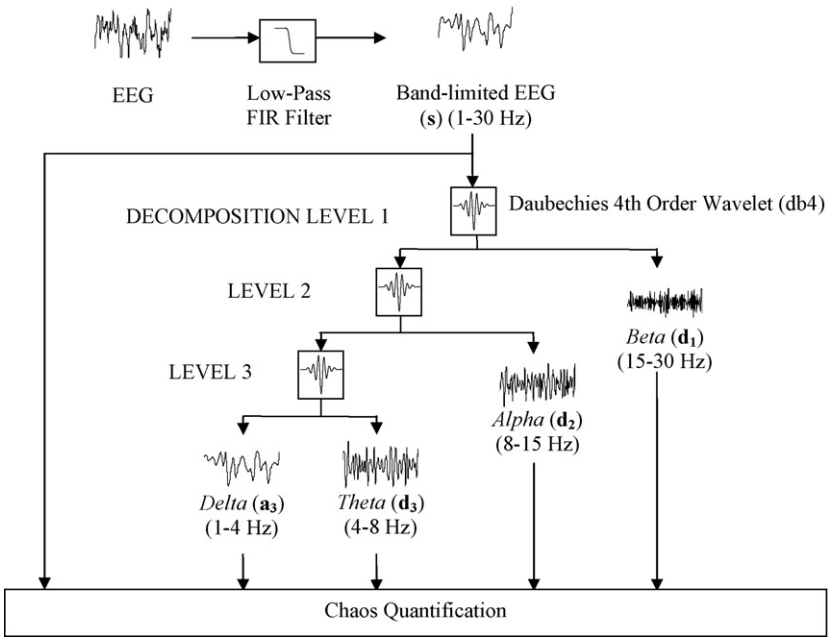


**Fig. 1.** EEG preprocessing and wavelet decomposition for sub-band extraction.

Although a decrease in EEG complexity in specific brain regions has been found in AD, no investigations have been reported regarding the localization of the decrease to specific EEG sub-bands. The EEG represents the effect of the superimposition of diverse processes in the brain and does not need to be treated as a unified system. The authors hypothesize that changes in underlying neuronal dynamics that are not evident in the original full-spectrum EEG may be amplified when each EEG sub-band is analyzed separately. In fact, the phenomenon of EEG slowing involves changes in the power of specific EEG sub-bands which appears to support this hypothesis. Recently, based on this very hypothesis, the authors developed a new wavelet-chaos methodology for analysis of EEGs and EEG sub-bands to identify potential parameters to be used in seizure and epilepsy detection [4].

The dataset used in this research consists of de-identified 19-channel EEGs (forehead ground and linked mandibles reference as shown in Fig. 3) from two different groups of subjects: healthy elderly (control group) and patients with a diagnosis of probable AD. The control group consists of seven subjects (average age of 71) with no history of neurological or psychiatric disorder. The AD group consists of 20 subjects (average age of 74) diagnosed with probable AD as per NINCDS-ADRDA and DSM-III-R criteria [30]. For both groups, the EEGs are collected under two conditions: eyes open and eyes closed. 8-Second EEG segments free from eye blink, motion, and myogenic artifacts are extracted from the EEG recordings. The EEGs (sampling rate of 128 Hz) obtained have previously been band-limited to the range of 1–30 Hz during the EEG recording (online) and preprocessing (offline) stages and will henceforth be referred to simply as the EEG. The range is sufficient to extract the four EEG sub-bands implicated in AD: *delta* (0–4 Hz), *theta* (4–7 Hz), *alpha* (8–12 Hz), and *beta* (13–30 Hz).

To obtain the four EEG sub-bands, the EEG signal is decomposed into progressively finer details by means of multi-resolution wavelet analysis (explained further in Adeli et al. [4]). After three levels of decomposition using 4th order Daubechies wavelet transform (Fig. 1), the EEG components retained are $\mathbf{a_3}$ (1–4 Hz), $\mathbf{d_3}$ (4–8 Hz), $\mathbf{d_2}$ (8–15 Hz), and $\mathbf{d_1}$ (15–30 Hz). Reconstructions of these four components using the inverse wavelet transform approximately correspond to the four physiological EEG sub-bands *delta*, *theta*, *alpha*, and *beta*. Minor differences in the boundaries between these components and the boundaries between the EEG sub-bands are of little consequence due to the physiologically approximate nature of the sub-bands.

The 19-channel EEGs collected under two conditions (eyes open and eyes closed) from seven healthy subjects and 20 AD patients yield a total of $19 \times 2 \times (7 + 20) = 1026$ EEGs. Similar to the original EEG, each sub-band is also subjected to chaos analysis to investigate the localization of the changes in CD and LLE to specific sub-bands of the EEG. As a result of the wavelet-chaos methodology (Figs. 1 and 2), each EEG is quantified by 10 parameters: CD, LLE, δCD, δLLE, θCD, θLLE, αCD, αLLE, βCD, and βLLE. In this notation, used in the remainder of this paper, the parameter prefix denotes the EEG sub-band from which the parameter is computed. Absence of a prefix indicates that the parameter is computed from the EEG. The five CD-based parameters represent the complexity and the five LLE-based parameters represent the chaoticity of the EEG and EEG sub-bands.

The statistical investigation is performed in three steps. First, for each of the ten parameters, a repeated measures factorial three-way Analysis of Variance (ANOVA) is performed with one between-subjects factor (Subject *Group*: Healthy or AD) and two within-subjects factors (*Condition*: Eyes Open or Eyes Closed; *Electrode Locus*). To identify parameters that potentially differentiate between healthy and AD subjects, main effects as well as interaction effects are investigated. The investigation in this step is not intended to localize differences in the parameter to any specific electrode locus. To achieve such a specific localization, a parameter is selected for further investigation only if the between-subjects factor main effect (or an interaction effect involving the between-subjects factor) is significant (significance level $\alpha = 0.05$).

Second, the efficacy of the *global* complexity and *global* chaoticity computed from the EEG and EEG sub-bands are investigated using a one-way ANOVA for distinguishing between the two EEG groups. In this step, the global complexity and chaoticity are estimated by averaging the values of the parameters selected in the first step across all 19 loci. In the third step, the *local* complexity and chaoticity in various brain regions are investigated to discover spatial patterns that could not be obtained from the global parameters.

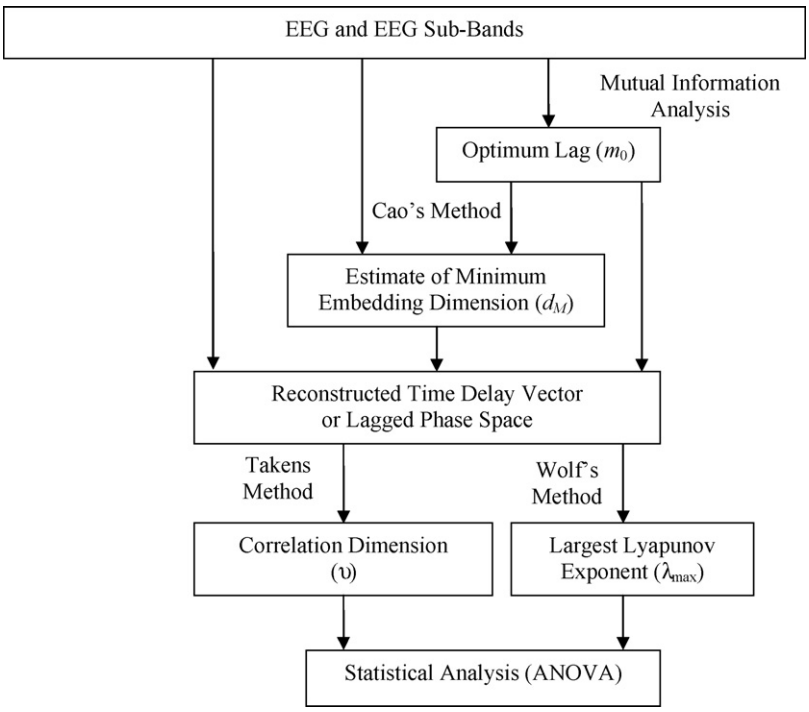


**Fig. 2.** Chaos quantification of EEG and EEG sub-bands.

To achieve this goal, the one-way ANOVA is performed separately for each locus based on the parameters selected in the first step. In the remainder of this paper, the parameter name will be preceded by the word *global* or *local* to indicate the source of the parameter. The electrode locus (Fig. 3) is used instead of the word *local* wherever specific local parameters are discussed. It is pointed out that the temporal aspect of the spatio-temporal analysis is implicit in the wavelet-chaos methodology and not a separate statistical investigation.

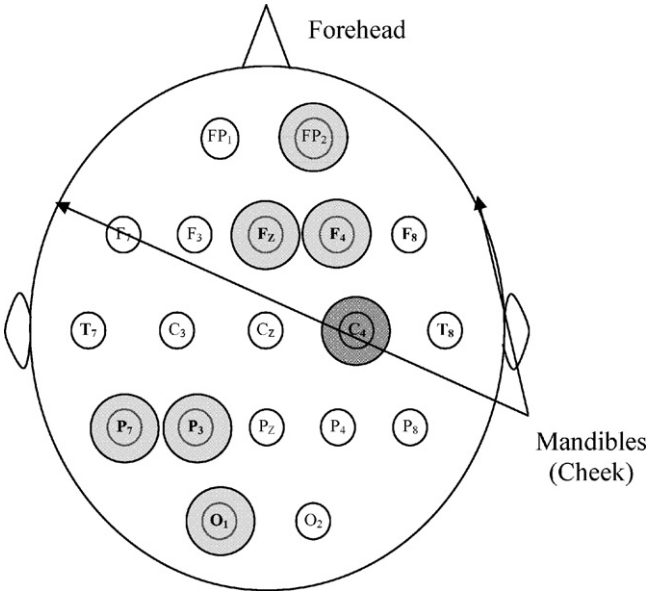


**Fig. 3.** Electrode loci (standard 10–20 electrode configuration for 19-channel EEG) showing the relative distribution of statistically significant parameters for chaoticity (light gray circles) and complexity (dark gray circle).

In the literature, only the complexity and chaoticity of the entire EEG represented by the parameters CD and LLE, respectively, have been investigated and reported to be reduced in AD. This assertion could not be corroborated in this research. The three-way factorial ANOVA revealed no significant differences ($\alpha = 0.05$; $p$-value < 0.05) in CD and LLE for the AD subjects compared with the healthy subjects regardless of the two within-subject factors—*condition* and *electrode loci* (i.e. no significant interaction effects were reported). Therefore, CD and LLE were not investigated further for specific loci or conditions.

The three-way factorial ANOVA revealed significant differences in θCD, θLLE, and δLLE between the two groups (main effects $p$-value < 0.05). No significant interaction effects were observed in θCD implying that the differences in the two groups were present regardless of the within-subject factors (*condition* and *electrode loci*). Significant *Group* × *Condition* × *Electrode Locus* interaction effects (in addition to the aforementioned main effects) were observed in θLLE and δLLE implying that in addition to the primary differences, the changes in spatial patterns (across electrode loci) between the eyes open and eyes closed conditions may be altered in the two groups, healthy and AD subjects. Significant *Group* × *Condition* interaction effects were observed in αCD and αLLE (although no main effects were observed) implying that although the parameters were not different in the two groups (healthy and AD subjects), the change in the parameters between the eyes open and eyes closed conditions may be altered in the two groups. In addition, significant *Group* × *Electrode Locus* interaction effects were observed in αLLE implying the possibility of altered spatial distributions (across electrode loci) of the parameter in the two groups. These observations warranted further investigation of the five parameters: θCD, θLLE, δLLE, αCD, and αLLE in order to localize the changes to specific electrode loci and the eyes open or eyes closed condition.

The efficacy of global complexity and chaoticity for discriminating between the two groups is investigated for both conditions: eyes open and eyes closed individually using one-way ANOVA. For the

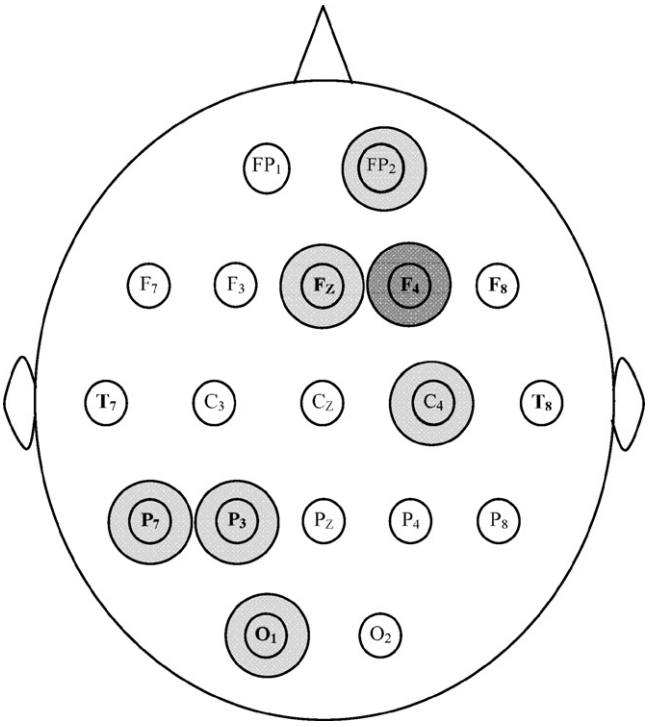


**Fig. 4.** Electrode loci showing the relative distribution of statistically significant parameters in the eyes closed condition (light gray circles) and eyes open condition (dark gray circle).

eyes open condition, no significant differences were observed in the *global* values of θCD, θLLE, δLLE, αCD, and αLLE. For the eyes closed condition, the *global* θLLE, and αLLE were found to be significantly reduced which could account for the significant *Group* × *Condition* interaction effects observed from the three-way factorial ANOVA. A surprising finding of this research is a significant increase in the *global* αCD which will be discussed in the next section.

To discover differences between the two groups of subjects with respect to changes in spatial patterns of complexity and chaoticity in the eyes open and eyes closed conditions individual one-way ANOVAs were performed for each electrode locus under the two conditions. In the eyes open condition, δLLE and θLLE computed from a specific electrode locus in the right frontal area ($F_4$) were significantly reduced in AD subjects. In the eyes closed condition, αLLE is significantly reduced in AD patients in the frontal midline ($F_Z$) and left occipital ($O_1$) areas. θLLE is significantly reduced in the right frontal ($FP_2$) and left parietal ($P_7$) areas and δLLE is significantly reduced in the left parietal ($P_3$) area. αCD was significantly increased at the $C_4$ locus (right central area). These findings could account for the significant *Group* × *Condition*, *Group* × *Electrode Locus*, and *Group* × *Condition* × *Electrode Locus* interactions observed from the three-way factorial ANOVA.

In Figs. 3 and 4, all loci where local parameters show significant differences are shaded in gray. The light and dark shades of gray will be explained in the following section. Overall, all changes are localized to the right frontal and left parieto-occipital regions.

The distribution of significant parameters is shown in Fig. 3, with the light gray circles representing chaoticity and the dark gray circles representing complexity. In general, the LLE appears to be much more consistent in distinguishing AD patients from healthy control subjects which appears to imply that the EEG chaoticity is reduced in AD subjects more consistently than EEG complexity. This phenomenon may not have been discovered previously due to two possible reasons. One, the method of computation of LLE used in this research is particularly suited to the characterization of non-linear dynamics of non-stationary EEG-like signals [4,5,29,19,13–15]. Two, the issue has not been studied previously from the perspective of EEG sub-bands.

The wavelet-chaos methodology developed in this research appears to be more effective for extracting meaningful markers of abnormality from the eyes closed condition than the eyes open condition. The relative distribution of significant parameters is shown in Fig. 4, with the light gray circles representing the eyes closed condition and the dark gray circles representing the eyes open condition.

From previous research [30], where only EEG complexity was studied, there appears to be some evidence that the differences between the two groups are more significant in the eyes open condition than in the eyes closed condition. In the earlier research, no significant differences were found in the eyes closed condition possibly because (1) individual sub-bands had not been investigated with respect to their underlying chaotic dynamics and (2) the chaoticity was not studied as a marker. In this research, the opposite was found to be true. For the eyes open condition, the CD appears to be of little use for differentiating AD patients from healthy controls irrespective of whether the global or local CD is employed. A possible explanation for this apparent contradiction may be that the conclusions of Pritchard et al. [30] are based on *dimensional complexity* which, although similar to the CD, is not computed by the Takens method employed in this research.

The availability of markers of abnormality obtained from eyes closed EEG has two advantages. First, there is no need for the patients to keep their eyes open and gaze steady during EEG recording to avoid eye blink and ocular artifacts. This is of special interest for the care of AD patients who find it very difficult to maintain such steady conditions. As a result, the process is quite uncomfortable for the patient and the EEG is nevertheless characterized by excessive artifacts. Second, due to the excessive artifacts in eyes open EEG, discrete artifact-free segments of the EEG often have to be patched together to obtain EEGs of the desired duration. This requires significant offline processing of the EEG. Moreover, the effects of the patching process on the subsequent chaos analysis have not been studied in detail. These effects, however, may be significant because of the implicit mismatch in characterizing *continuous* brain dynamics by *discontinuous* EEGs.

Why is eyes closed EEG better than eyes open EEG for distinguishing AD patients from healthy control subjects? There may be two possible explanations for this. One, the wavelet-chaos methodology and the sub-band analysis developed in this research accurately characterize the non-linear dynamics of non-stationary EEG-like signals with respect to the EEG chaoticity. As a result, new potential markers of abnormality were discovered in this research. Two, the neurological processes, especially those governing the observed decrease in EEG chaoticity, in the eyes closed condition lead to differences between AD patients and healthy control subjects. The eyes closed condition represents the internal brain dynamics without the modulation associated with visual attention and the resultant cognitive processing in the eyes open condition. It is possible that exposure to external stimuli, raises the chaoticity of the brain in AD to (or close to) the level of a healthy brain of approximately the same age, thus making the two groups indistinguishable on this basis.

Prior to this research, to the best of the author's knowledge no sub-band analysis had been performed on the chaotic dynamics of EEGs obtained from patients with probable AD. Since the EEG is an overall representation of brain dynamics, it opens up the possibility that the observed changes in the parameters quantifying chaos in the EEG are actually the result of the superimposition of multiple processes underlying the EEG. In this research, these

underlying processes are investigated using the component physiological sub-bands of the EEG which can be assumed to represent these processes at a finer level.

It is found that when the statistical analysis is based on the entire EEG, the LLE or the CD cannot be used as a discriminating parameter between the two groups. However, when the statistical analysis is performed on the EEG sub-bands, it is observed that the CD as well as the LLE from certain physiological sub-bands and loci may be employed to distinguish between the groups. As a result of this investigation, it is concluded that changes in the dynamics are not spread out equally across the spectrum of the EEG, but instead, are limited to certain frequency bands. Moreover, the changes are not globally spread over the entire brain but localized to specific electrode loci.

In this research, 11 potential markers of abnormality were discovered using the wavelet-chaos methodology, 2 in the eyes open condition ($F_4$ δLLE and θLLE) and 9 in the eyes closed condition (*global* θLLE, αCD, and αLLE; and $FP_2$ θLLE, $P_7$ θLLE, $P_3$ δLLE, $C_4$ αCD, $F_Z$ αLLE, and $O_1$ αLLE). Other markers such as the neural complexity in the eyes open condition dubbed *dynamic responsivity* have been reported in the literature [30]. These markers may well represent different aspects of AD and can be used to complement each other in clinical applications. The availability of multiple potential discriminating parameters will result in increased accuracy of EEG classification for AD patients. Based on these potential markers of abnormality, the authors are currently researching the application of the presented methodology for diagnosis of AD in a clinical setting.

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