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Identification of Resting and Active State EEG Features of Alzheimer's Disease using Discrete Wavelet Transform

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Abstract—Alzheimer's disease (AD) is associated with deficits in a number of cognitive processes and executive functions. Moreover, abnormalities in the electroencephalogram (EEG) power spectrum develop with the progression of AD. These features have been traditionally characterized with montage recordings and conventional spectral analysis during resting eyes-closed and resting eyes-open (EO) conditions. In this study, we introduce a single lead dry electrode EEG device which was employed on AD and control subjects during resting and activated battery of cognitive and sensory tasks such as Paced Auditory Serial Addition Test (PASAT) and auditory stimulations. EEG signals were recorded over the left prefrontal cortex (Fp1) from each subject. EEG signals were decomposed into sub-bands approximately corresponding to the major brain frequency bands using several different discrete wavelet transforms and developed statistical features for each band. Decision tree algorithms along with univariate and multivariate statistical analysis were used to identify the most predictive features across resting and active states, separately and collectively. During resting state recordings, we found that the AD patients exhibited elevated D_4 (~4–8 Hz) mean power in EO state as their most distinctive feature. During the active states, however, the majority of AD patients exhibited larger minimum D_3 (~8–12 Hz) values during auditory stimulation (18 Hz) combined with increased kurtosis of D_5 (~2–4 Hz) during PASAT with 2 s interval. When analyzed using EEG recording data across all tasks, the most predictive AD patient features were a combination of the first two feature sets. However, the dominant discriminating feature for the majority of AD patients were still the same features as the active state analysis. The results from this small sample size pilot study indicate that although EEG recordings during resting conditions are able to differentiate AD from control subjects, EEG activity recorded during active engagement in cognitive and auditory tasks provide important distinct features, some of which may be among the most predictive discriminating features.

Keywords—EEG, Alzheimer's disease, Discrete wavelet transform, Active brain states, Decision tree.

INTRODUCTION

Alzheimers disease (AD) is by far the most common form of dementia gradually leading to death of patients. It affects about 5.4 million Americans and almost 50% of those older than 85. It is the third most expensive disease and sixth leading cause of death in the United States and estimates that the disease will triple by 2050.[31] AD is a progressive neurodegenerative disease affecting the hippocampus, neocortex, and other brain regions associated with memory and executive functions as well as neuromodulatory systems including the basal forebrain cholinergic neurons that regulate cortical neuron activity.[15] While no cure currently exists, early detection and differentiation of AD from normal aging processes are critical to begin early intervention to delay the onset of symptomatology of AD and begin palliative strategies as well as develop treatments that prevent AD pathophysiology.[10]

The electroencephalogram (EEG) reflects the averaged electrical activity of large numbers of cortical neurons associated with different neural information processing of brain regions. Currently, there is no known objective method of diagnosing AD and the use

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of EEG as a diagnostic tool continues to be challenged given that most of the existing methods are not analytically or clinically validated and require significant improvement.[14] However, because of its non-invasive and safe properties, EEG signal analysis remains a potential tool that may aid in the early diagnosis of AD. Single channel and multi-channel quantitative EEG signal analysis has traditionally used Fast Fourier Transform (FFT) power spectral approaches to extract frequency information as a potential determinant of the discriminating features of AD.[4,7,14,21] Generally, increased power in the 4–7 Hz (θ frequency band) range is observed early in the progression of AD. While further progression is associated with initial decreases in α (8–13 Hz) and β (13–30 Hz) bands followed by increases in the low frequency δ (1–4 Hz) band power.[23]

Although FFT based methods are computationally efficient, the non-stationary and discontinuous properties of EEG signals following artifact removal are problematic for traditional FFT approaches.[3] Meanwhile, various researchers have shown that time domain nonlinear dynamics approaches offer some promise[21] but they are computationally complex, require extensive experience, and have not yet demonstrated reliable diagnostic power in their present form.[29] Wavelet-based transformation[9] of EEG signals to represent EEG power distribution over both time and frequency continues to be a promising approach and is more suitable for spectral analysis for brain disease detection when compared to FFT.[3,5]

There are two types of wavelet analysis: continuous wavelet transform (CWT) and discrete wavelet transform (DWT). Both DWT and CWT have been used in EEG analysis and classification in the literature. Statistical features are extracted at different wavelet decomposition levels and used with neural network based methods for classification of abnormal vs. normal subjects.[19,20,28] DWT is generally more computationally efficient and more widely used than CWT.[2] To our knowledge, very few published studies have used DWT to directly extract EEG features from patients with a clinical diagnosis of AD. Known studies include Polikar *et al.*[26] who identified discriminating event related potentials (ERP) of the EEG using an auditory oddball paradigm. The authors identified and classified ERP features corresponding to 1–8 Hz (δ and θ bands) and concluded that DWT appears to be a feasible approach to aid with the early diagnosis of AD. In another study, Wan *et al.*[33] investigated the quantitative EEG power spectrum of Chinese Han ethnic AD patients recorded during resting eyes-closed (EC) state. They reported that AD patients' EEG spectrum has a higher power in slow activities (0–2 Hz) and lower power in fast activities (16–32 Hz) and concluded that AD patients in China, consistent with the published literature, show evidence of specific spectral EEG changes. A third study presented a wavelet-chaos methodology to find potential markers of AD abnormality.[1] This paper reported markers limited to δ and θ spectral frequency bands.

Although AD is characterized by progressive impairment in cognitive and memory processes, resting EC or resting eyes-open (EO) conditions are commonly used during clinical EEG recordings; e.g., Elgendi *et al.*[14] These data have provided valuable information for differentiating AD patients. Nonetheless, we hypothesize that EEG signals recorded during activated states of the brain can provide unique discriminating features of AD, thus leading to a more accurate assessment of brain health and function.[17] To test this hypothesis, we collected EEG recordings from AD and age-matched control subjects (CTL) under both resting conditions (EC and EO) and during a number of cognitive and sensory tasks including auditory stimulations, the Paced Auditory Serial Addition Test (PASAT), and the CogState brief battery of tasks to assess attentional processes, learning, working memory, and information processing speed.[18,24] DWT with 5 different wavelet functions were used for feature extraction from EEG signals in five decomposition levels, where at each decomposition level statistical features of the signal were calculated. The significant discriminating features of AD were determined using both univariate and multivariate analysis of variance (ANOVA) methods.[22] Decision tree algorithms were then employed as a classification method to identify the most dominant EEG features of AD in resting and activated states, separately and collectively.

METHODS AND MATERIALS

Characterization of a Single Lead Dry Sensor EEG Headset

A novel EEG headset device was modified for use in a clinical context to record a 128 samples/s 10-bit data stream transmitted from a single EEG sensor placed at position Fp1 (based on a 10–20 electrode placement system). Differential voltage signals relative to mastoid on the left ear were amplified *via* an application-specific integrated circuit (ASIC) containing an instrumentation differential amplifier followed by an analog filter with common mode rejection at 60 Hz. Two stainless steel mastoid electrodes (reference and ground) were embedded in the left ear cup of the headset for compression contact to the left ear of the subject. After analog to digital conversion with a 10-bit

unsigned analog-to-digital-converter (ADC), digital EEG signals passed through an ASIC digital signal processor before being transmitted *via* Bluetooth to a nearby computer. The Bluetooth stream was parsed in the computer according to the manufacture's technical specifications and verified by independent bench top assessment. To assess the analytical performance of the hardware/software system, we input various test signals generated from a NIST traceable function generator. The output reference signals were passed through a voltage divider consisting of two metal film precision resistors of 100 Ω and 1 MΩ impedance. This 1:10^4 voltage reduction enabled a 1.0 V output to become 100 μV. Sine waves of 5–30 Hz at 5 Hz increments were hardwired into the headset and the resulting signals recorded and analyzed. We determined that the frequency response of the system was less than 0.25 Hz spectral band bin width. In addition, we assessed the amplitude response of the system by stepping the signal generator output down by a factor of 2 and observed an excellent fourfold decrease in power (due to their inverse squared relation).

Additional analytical bench studies were conducted to assess the signal to noise ratio (SNR) of the system in both an open-circuit and closed-circuit configuration. In particular, 15 Hz reference signals were hardwired into the headset for 30 s blocks at varying amplitudes and compared to 30 s recordings when the lead from the function generator was removed from the active sensor. All signal-to-noise ratio levels were above 16 db as assessed in both the voltage/time domain as well as the Fourier transformed frequency domain. Typical signal-to-noise ratio measures were in excess of 30 db showing excellent frequency discrimination.

Bench experiments were conducted to evaluate the least significant bit by varying the input signal strength between two values in smaller and smaller increments until the modulation could no longer be detected by the EEG headset and recording system. It was observed that single μV signal changes to the input electrodes could be detected as a single bit change in the ADC over a 30 s EEG recording block.

To compare the headset to traditional clinical EEG equipment, we simultaneously recorded arbitrary waveform signals loaded into the buffer of an arbitrary waveform/function generator hardwired in parallel to a Compumedics Neuroscan NuAmps system and our device. Reference EEG traces downloaded from the UCSD website[11] were uploaded into the buffer and spooled out. After independent analysis of the recorded 10,000 samples/s, 24-bit ADC signal from the Fp1 channel of the NuAmps system and the 128 samples/s, 10-bit ADC output from our device, the gross spectral response was indistinguishable except for frequencies below 2 Hz. Thus, the analytical bench assessment of the customized headset device demonstrated excellent ability to accurately record EEG signals in the 1–100 μV and 2–30 Hz ranges.

Confirmation of Physiology in Human Subjects

We investigated the integrity of EEG recordings by the device placed on human subjects. As the active electrode sits at position Fp1 and mastoid was referenced *via* three surface contact electrodes on the left ear, the volume of conduction being sampled is large and covers the left frontal cortex. Typical EEG artifacts in both live and recorded traces were critically observed such as eye blink, EMG derived signals, tongue movement, eye roll and teeth clench. Importantly, when a human subject was asked to maintain a resting condition in either the EO or EC conditions, one would observe well defined EEG signals. To explicitly confirm this, we recorded EEG signals sequentially from the same subject in both the resting EC and EO conditions. After artifact detection and signal processing using spectral analysis with sliding windows to create a Power Spectral Density (PSD) across all frequency bins from 1.0 to 30.0 Hz in 0.25 Hz steps, we then computed the EC/EO ratio between the two power spectra on an individual frequency bin by bin basis. As expected, a statistically significant prominent peak of α rhythm activity was observed centered around 10 Hz in the EC condition.[16] While examining the bin by bin ratio of EC/EO powers, we often observed that this α rhythm peak was seven to tenfold higher in the EC condition relative to the EO condition.

In order to assess other basic elements of the *in vivo* performance of the device on adult human subjects, we conducted several reproducibility studies where we measured both EC and EO conditions for 2 min at approximately the same time of day (to avoid circadian rhythm effects) and food/hydration state. After 5 days of monitoring, we computed a relative coefficient of variation of between 10 and 30% across the δ, θ, α and β bands recorded in the same subject at the same time of day over five independent days.

Human Subjects and Clinical Study Design

The objective of this study was to identify the discriminant features of EEG signals extracted from Alzheimers disease (AD) patients compared to healthy age-matched control subjects. Up to 250 subjects were to get stratified into several cohorts. Inclusion criteria included: (1) healthy normal's ages; (2) diagnosis of probable AD according to the NINCDS-ADRDA Alzheimer's criteria; (3) Mini-mental state examination

(MMSE) score 20–27; (4) diagnosis of mild cognitive impairment (MCI) according to Peterson criteria; (5) availability of a caregiver for AD and MCI subjects. Study exclusion criteria included: (1) diagnosis of significant neurological disease other than AD; (2) history of strokes, seizures, or traumatic brain injuries; (3) Chronic pain; and (4) use of high doses of sedating or narcotic medications. Other demographic items noted were date of birth, gender, ethnicity, education, relevant medical history, current prescription and non-prescription medications, nutritional supplements, and alcohol/tobacco use.

All Personal Health Information (PHI) was retained at Palm Drive Hospital and no PHI was provided to any collaborator for HIPAA Compliance. Subjects were assigned a random/sequential subject number which was the only identifier used to analyze the demographic, independent, and subsequently dependent variables of the study. All study data were encrypted *via* AES-256 bit encryption at the site of data acquisition before transport to central servers whenever any information was present in the data file. We also employed a multi-step process whereby all parties remained blind until the final extracted EEG features data table was produced and circulated internally to the collaborating members.

Twenty six subjects were enrolled, one withdrew due to non-study related reasons and one did not qualify as Alzheimer's Disease (AD) or control (CTL) but was diagnosed with MCI. Data from the remaining 24 subjects were considered, including 10 AD and 14 age-matched CTL. The subject information for these 24 individuals are presented in Table 1.

TABLE 1. Subject demographics and health information.

Subject no.	Gender	Age	Handedness	Clinical diagnosis
1	F	57	R	CTL
2	F	86	R	CTL
3	F	54	R	CTL
4	F	68	R	CTL
5	M	63	L	CTL
6	F	83	R	AD
7	F	83	R	CTL
8	F	67	R	CTL
9	M	82	R	AD
10	M	69	R	CTL
11	M	75	R	CTL
12	F	74	R	CTL
13	F	75	R	CTL
14	F	57	R	CTL
15	M	81	R	CTL
16	F	85	R	CTL
17	M	84	R	AD
18	F	75	R	AD
19	M	80	R	AD
20	M	62	R	AD
21	M	73	R	AD
22	M	86	R	AD
23	M	76	R	AD
24	F	89	R	AD

Behavioral Tasks Within the Battery of Assessment

Wearing the device, subjects were asked to sit in a comfortable chair and open and close their eyes for nearly 2-min blocks, alternately recording 3 sessions of resting EC and 3 sessions of resting EO. They were then tasked with the four components of the CogState Research (Melbourne, Australia) brief battery: Detection, Identification, One Card Back, and One Card Learning tasks. CogState's brief battery is a computerized neuropsychological battery designed to be sensitive to the cognitive impairments that characterize mild-to-moderate AD yet simple enough for patients to complete without requiring great support or assistance. The Detection task is a measure of simple reaction time and has been shown to provide a valid assessment of psychomotor function in healthy adults with schizophrenia. The Identification task is a measure of choice reaction time and has been shown to provide a valid assessment of visual attention. The One Card Learning and One Card Back cognitive tasks are valid measures of working memory.

Next, the PASAT task of 60 auditory addition trials was conducted at up to 3 different lag intervals of trial. PASAT is a measure of cognitive function that specifically assesses auditory information processing speed and flexibility, as well as calculation ability. Subjects are asked to listen to a series of numbers and are requested to add consecutive pairs of numbers as they listen. There is no visual component to this task.

Brief auditory binaural beat stimulations (90 s, 50–75 db) with differential beat frequencies of 6, 12, and 18 Hz were conducted next, followed by one final block of each resting EC and EO to close the data collection paradigm. Table 2 shows the summary description of each task and their typical duration for all the subjects. There were normally a short break between recording sessions. Although there were a total of 18 possible recording tasks, a large number of subjects did not complete the PASAT 1.6 (s) interval (Task 13) and hence the data from this task was not included in the analysis.

EEG Signal Quality and Pre-processing

The rechargeable battery powered Bluetooth enabled EEG headset eliminated frequently observed artifacts including line noise. However, it was critical to detect and eliminate other artifacts such as eye-blinks

TABLE 2. Description and duration of the EEG recording states.

Number	Description	Duration (s)
1	First Eyes-Closed (EC1)	90–120
2	First Eyes-Open (EO2)	90–120
3	Second Eyes-Closed (EC3)	90–120
4	Second Eyes-Open (EO4)	90–120
5	Third Eyes-Closed (EC5)	90–120
6	Third Eyes-Open (EO6)	90–120
7	Cognitive task 1: Attention (CG1)	90–120
8	Cognitive task 2: Identification (CG2)	90–120
9	Cognitive task 3: One Card Learning (CG3)	180–240
10	Cognitive task 4: One Card Back (CG4)	180–240
11	PASAT: 2.4 (s) intervals (P-2.4)	90
12	PASAT: 2.0 (s) intervals (P-2.0)	90
13	PASAT: 1.6 (s) intervals (P-1.6)	90
14	Auditory Stimulation, Left = 397, Right = 403, 6 Hz (AS1)	90
15	Auditory Stimulation, Left = 394, Right = 406, 12 Hz (AS2)	90
16	Auditory Stimulation, Left = 391, Right = 409, 18 Hz (AS3)	90
17	Fourth Eyes-Closed (EC7)	90–120
18	Fourth Eyes-Open (EO8)	90–120

in the EEG signal. These artifacts, frequent at Fp1 location, often have high amplitudes relative to brain signals. Thus, even if their appearance in the EEG data is not frequent, they may bias the results of a given block of data or experiment.[12] In this study, any DC offset of the EEG signal was subtracted and an artifact detection pre-processing algorithm was used to eliminate large amplitude artifacts greater than 4.5σ (standard deviation). An algorithm was developed to detect such artifacts, nullify, and then reconstruct the nulled samples using FFT interpolation of the trailing and subsequent recorded data. However, amplitude-based artifact detection method sometimes fail to detect low frequency artifacts such as small eye blinks.[12] Hence, we recursively applied our artifact detection method to the modified signal up to three times. This method eliminated the remaining low frequency artifacts with very high reliability considering that the EEG signals are generally normally distributed (i.e., 1 in 49,053 samples are expected to be out of range for the filtered signal while the sample size is in the 10,000–20,000 range). For illustrative purposes, Fig. 1 shows all the recorded EEG blocks concatenated one after the other for subject number 11, a CTL subject, in arbitrary units from the 10-bit analog-to-digital converter (ADC) before and after artifact detection. The enlarged area on the left is part of the second recording state EO2 where all eye blinks have been eliminated. The enlarged area on the right shows part of the 18 Hz auditory stimulation, AS3, where a few eye blinks plus a single artifact with a very large amplitude have been removed. The results show improvement over our previous artifact detection.[17] However, large amplitude signals in the PASAT recordings have not been filtered out due to larger σ during these sessions which are due normal physiological activities since subjects respond vocally.

The headset sample rate was specified at $f_s = 128$ Hz by the manufacturer. However, the effective sample rate was closer to $f_s = 125$ Hz in our experiments. Frequencies below 1 Hz and above 60 Hz (near Nyquist frequency) were filtered out. Furthermore, we only analyzed frequencies between 2 and 30 Hz due to the demonstrated reliability of the device; see section "Characterization of a Single Lead Dry Sensor EEG Headset".

Discrete Wavelet Transform Feature Extraction

Discrete wavelet transform analyzes the signal at different temporal resolutions through its decomposition into several successive frequency bands by utilizing a scaling and a wavelet function associated with low-pass and high-pass filters. The original EEG signal $x(t)$ forms the discrete time signal $x[i]$, which is first passed through a half-band high-pass filter, $g[i]$, and a low-pass filter, $h[i]$. Filtering followed by sub-sampling constitutes one level of decomposition and can be expressed as follows[26]:

$$d_1[k] = \sum_n x[i].g[2k - i], \tag{1}$$

$$a_1[k] = \sum_n x[i].h[2k - i], \tag{2}$$

where $d_1[k]$ and $a_1[k]$ are level 1 *detail* and *approximation* coefficients at translation k, which are the outputs of the high-pass and low-pass filters after the sub-sampling, respectively. This procedure, called sub-band coding, is repeated for further decomposition as many times as desired or until no more sub-sampling is possible. At each level, it results in half the time resolution (due to sub-sampling) and double the frequency resolution (due to filtering), allowing the signal to be analyzed at different frequency ranges with different resolutions.

Of the many families of mother wavelets, the Daubechies family[9] possesses a number of characteristics that are ideal for EEG analysis, including (1) the well understood and smoothing characteristics of Daubechies2 (db2)[19] and (2) detection of changes in

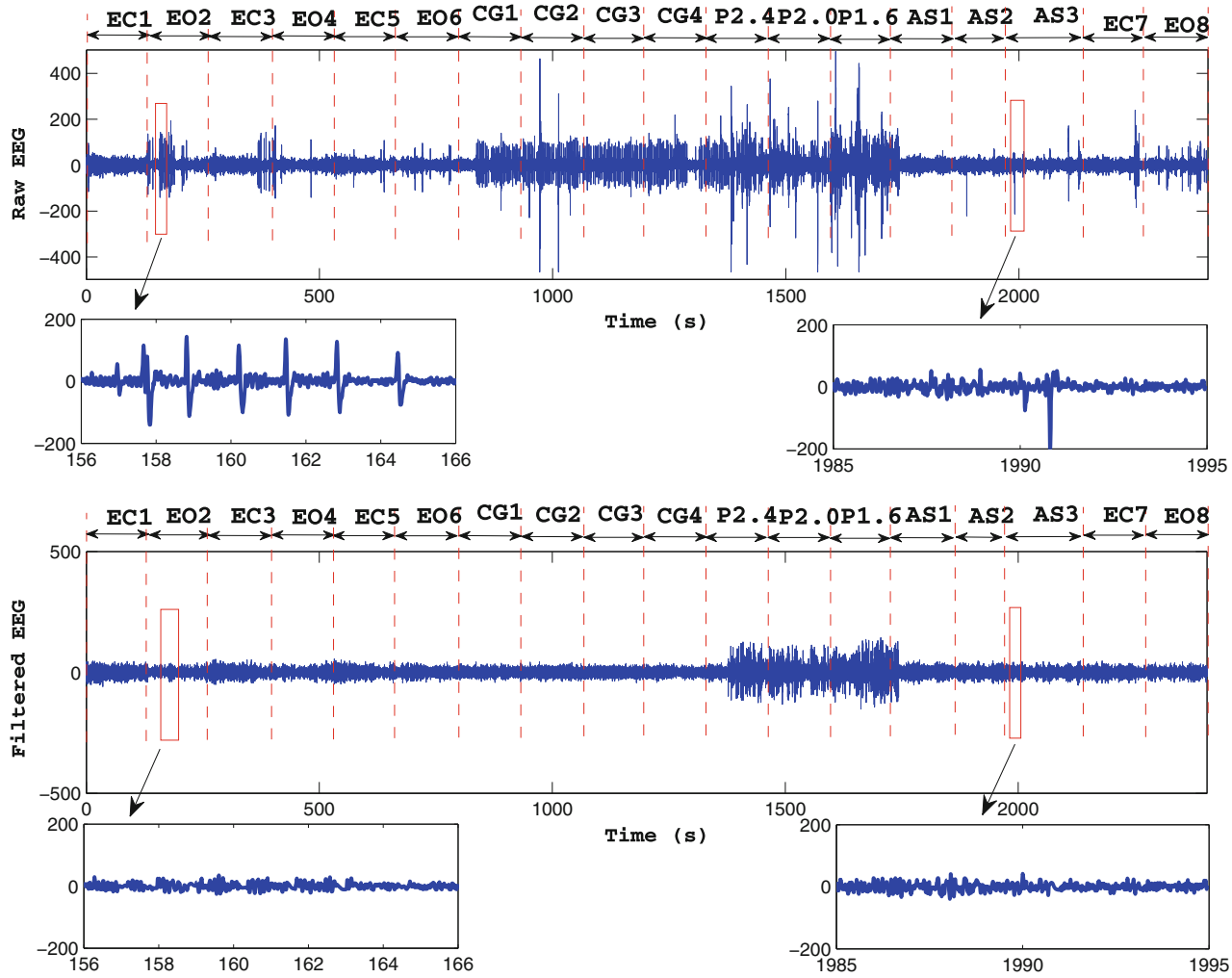

FIGURE 1. Raw EEG signal of subject 11 before (top) and after (bottom) artifact detection pre-processing. Y-axis is arbitrary units from the onboard 10 bit unsigned ADC.

EEG important for detecting epileptiform activity.[2] In this study, we used five different mother wavelets from the Daubechies family: db2, db4, db6, db8, and db10.

We performed five levels of decomposition resulting in D_1 (approximately related to the γ spectral frequency band) through D_5 (approximately related to the upper δ spectral frequency band) and A_1 through A_5 (approximately related to lower δ spectral frequency band), as shown in Fig. 2. Table 3 shows the exact sub-band frequency ranges and their corresponding approximate EEG major spectral frequency bands. However, the recording device was only validated for 2–30 Hz frequency range. Hence, we excluded D_1 (~γ) and A_5 (~lower δ) sub-band features in our analysis. As a result, the effective sub-bands used in this study were D_2–D_5.

Having created the DWT sub-bands of EEG signal, we can extract the common statistical features from the DWT analysis.[20,30,32] In this study, we selected the the mean power, minimum, maximum, as well as standard deviation (SD), skewness, and kurtosis of the wavelet coefficients as candidate extracted features. The mean power of the wavelet coefficients was computed as follow:

$$P_j = \frac{1}{n}\sum_{i=0}^{n-1} |x_i|^2, \quad j = 1, \ldots, N, \tag{3}$$

where x_i's are the computed coefficients of the signal at each sub-band, n is the number of computed coefficients at each sub-band, and N is the total number of sub-bands. These values were computed at each level of DWT decomposition separately for each recording block from each task of each subject. Note that, we did not consider the mean values since we had subtracted the mean before processing the data.

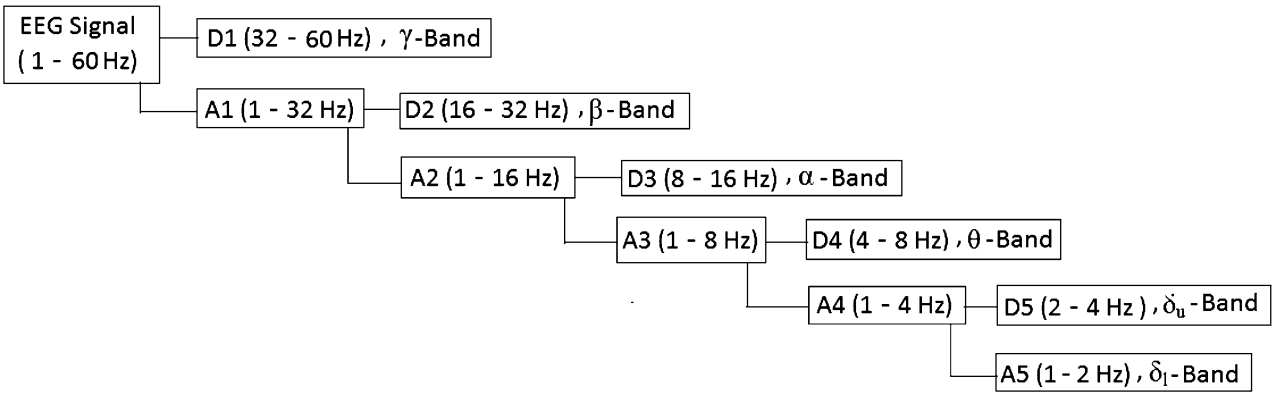

FIGURE 2. Five level decomposition of an EEG signal; D_1–D_5 and A_5 are the DWT representation of the signal.

TABLE 3. DWT sub-band frequencies and the corresponding approximate major brain frequency bands.

Sub band	Frequency range (Hz)	Corresponding EEG frequency band (Hz)
D_1	30–60	γ (>30)
D_2	15–30	β (13–30)
D_3	7.5–15	α (8–13)
D_4	3.75–7.5	θ (4–8)
D_5	1.875–3.75	$\delta_{\{u}$ (2–4)
A_5	1–1.875	$\delta_{\{l}$ (0–2)

Univariate and Multivariate Statistical Testing of DWT Features

We were unable to use common statistical testing methods that rely on normal distribution (e.g., *t*-Test) to compare the signals from the 10 AD patients with the 14 CTL subjects since the extracted feature data were not normally distributed. Furthermore, transformation techniques were not successful. Thus, we chose the non-parametric Wilcoxon rank-sum test, which is the two sample version of the Kruskal–Wallis one-way analysis of variance (ANOVA) by ranks and is a method for testing whether samples originate from the same distribution. The null hypothesis of the Wilcoxon rank-sum test is that the populations from which the samples originate have the same median. Since Wilcoxon rank-sum test is a non-parametric method, it does not assume a normal distribution.[13]

We used multivariate ANOVA[22] to investigate not only the null hypothesis but also whether or not the features are highly correlated and increase the reliability of the statistically significant features. We grouped the six features (mean power, minimum, maximum, SD, skewness, kurtosis) corresponding to each DWT decomposition (D_2 through D_5) as the six dependent variables of multivariate analysis.

Subject Classification Using Decision Tree Analysis of Extracted Features

Since several significant features were identified in our study from Wilcoxon rank-sum test, we wanted an objective algorithm to identify the most dominant and reliable discriminating features of AD patient EEG signals in our study. Therefore, we applied a widely used classification method called decision tree analysis.[25] Decision tree analysis holds several advantages over traditional supervised methods, such as maximum likelihood classification. It does not depend on assumptions of distributions of the data and therefore is a non-parametric method. Another valuable advantage of decision tree is its ability to handle missing values, which is a very common problem in dealing with biomedical data.[34,35] However, a disadvantage of the decision tree algorithm for our application is that it does not account for univariate statistical significance of the utilized features.

The most important aspect of a decision tree induction strategy is the split criteria, which is the method of selecting an attribute test that determines the distribution of training objects into sub-sets upon which sub-trees are consequently built.[25] In this study, we used three well-known split criteria: Gini, Twoing, and maximum deviance reduction (or entropy) indexes. The Gini index, I_G, is defined as[35]:

$$I_{G(t)} = \sum_i p_i(1 - p_i) \tag{4}$$

where p_i is the relative frequency of class i at node t, and node t represent any node at which a given split is performed. p_i is determined by dividing the total number of observations of the class by the total number of observations. The Twoing index, I_T, is defined based on the proportion of the t population sent to the left, P_L, and right, P_R, tree branches such that $P_L + P_R = 1$[8]:

$$I_{T(t)} = \frac{P_L P_R}{4}\left(\sum_i |p_{i,L} - p_{i,R}|\right)^2 \quad (5)$$

where $p_{i,L}$ and $p_{i,R}$ are the relative frequencies of class i at left and right nodes, respectively. The maximum deviance reduction index, also known as entropy, I_E, is defined as

$$I_E(t) = -\sum_i p_i \log p_i \quad (6)$$

where p_i is the relative frequency of class i at node t.

RESULTS

Choice of mother wavelet function is the most important factor for a reliable DWT analysis. Therefore, we determined EEG features of AD patients compared to CTL subjects across five candidate wavelet functions from the Daubechies family. The number of statistically significant EEG features of AD patients compared to CTL subjects, identified by the five different wavelets, are shown in Table 4, where many features were common among the different wavelet functions. We then performed univariate and multivariate ANOVA for all features, applied three different split criteria, and chose the best decision tree based on reliability of the utilized features.

Discriminating DWT Features of AD Patients

We initially applied univariate statistical testing to identify the statistically significant discriminant DWT extracted features of AD patients compared to CTL subjects. Given that data within the six statistical measures (minimum, maximum, SD, skewness, kurtosis, and mean power) were not normally distributed, the non-parametric Wilcoxon rank-sum test for one-way ANOVA was used. Table 5 provides an overview of the db4-based DWT coefficient features extracted during these tasks that are statistically different with their corresponding false positive rate p values. Overall, the second EO state (EO4) yielded the most number of statistically significant features followed by the third EO state (EO6) and auditory stimulation at 18 Hz (AS3). Note that, the differences in the first and last round of resting states may be explained by the fact that the subjects may not have initially been fully resting or later were perhaps tired and restless at the end of recording sessions. The other four resting states combine to yield similar results to their individual recording blocks.

TABLE 4. Number of statistically significant features derived by different Daubechies family of wavelets.

Mother wavelet	No. of significant features
Daubechies2 (db2)	19
Daubechies4 (db4)	28
Daubechies6 (db6)	21
Daubechies8 (db8)	26
Daubechies10 (db10)	25

Statistically significant features of AD patients observed in the resting EO and EC are consistent with published literature where increased δ and θ activities and lower β activities have been reported for AD patients.[21,23] To illustrate the performance of DWT with db4 wavelet function, Figs. 3 and 4 show the raw EEG signal recorded during EO4 followed by the signals after each level of decomposition for subjects 5 (a CTL subject) and 25 (an AD subject), respectively. The higher D_5 (~δ) and D_4 (~θ) activities and lower D_3 (~α) and D_2 (~β) activities of the AD subject compared with the CTL subject are clearly observed through the amplitudes of the corresponding signals.

Note that, we initially determined EEG features using the traditional short-time FFT with sliding windows of 8-s duration. We then calculated the mean powers, standard deviations, skewness, and kurtosis for all the frequency ranges corresponding to the major brain frequency bands as listed in Table 3. However, we were unable to determine any of the widely reported discriminating features and determined above using DWT except higher θ mean power.

Among the active states, the discriminating features during auditory stimulation at 18 Hz all belonged to the wavelet coefficient in the D_3 scale range. Other discriminating features included skewness of D_2 and D_3 during the One Card Learning cognitive task (CG3), skewness of D_3 during Attention (CG1) task, and kurtosis of D_5 during PASAT with 2.0 s interval (P2.0).

Multivariate ANOVA confirmed the null hypothesis for these features but could not reject the hypothesis that these features lie on the same line. In other words, the six dependent variables, features of the wavelet coefficients within the same sub-band, may not be independent discriminants. Thus, the wavelet coefficient features within the same sub-bands are highly correlated and we cannot prove that any of the recordings blocks displayed in Table 5 has more than one independent discriminating feature. In general, the low number of independent statistically significant features is likely attributed to the small sample size of the study and limited associate power.

In this study a large number of pairwise statistical tests ($n = 408$) have been performed. Hence, we attempted to apply different variations of Bonferroni correction and False Discovery Rate for multiple comparisons. However, we were unable to observe any

TABLE 5. Statistically significant (db4) DWT EEG features of AD subjects based on Wilcoxon rank-sum test and their corresponding false positive *p*-values.

	EC1	EO2	EC3	EO4	EC5	EO6	CG1	CG2	CG3	CG4	P2.4	P2.0	AS1	AS2	AS3	EC7	EO8
MP D_2	–	–	.03	–	.04	–	–	–	–	–	–	–	–	–	–	–	–
MP D_3	–	–	–	–	–	–	–	–	–	–	–	–	–	–	.03	–	–
MP D_4	–	–	–	.009	–	–	–	–	–	–	–	–	–	–	–	–	–
MP D_5	–	–	–	.0008	–	.046	–	–	–	–	–	–	–	–	–	–	–
Min D_2	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Min D_3	–	–	–	–	–	–	–	–	–	–	–	–	–	–	.033	–	–
Min D_4	–	–	–	.022	–	–	–	–	–	–	–	–	–	–	–	–	–
Min D_5	–	–	–	.022	–	–	–	–	–	–	–	–	–	–	–	–	–
Max D_2	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Max D_3	–	–	–	–	–	–	–	–	–	–	–	–	–	–	.02	–	–
Max D_4	–	–	–	.035	–	–	–	–	–	–	–	–	–	–	–	–	–
Max D_5	–	–	–	.013	–	–	–	–	–	–	–	–	–	–	–	–	–
SD D_2	–	–	.035	–	–	.04	–	–	–	–	–	–	–	–	–	–	–
SD D_3	–	–	–	–	–	–	–	–	–	–	–	–	–	–	.033	–	–
SD D_4	–	–	–	.009	–	–	–	–	–	–	–	–	–	–	–	–	–
SD D_5	–	–	–	.008	–	.046	–	–	–	–	–	–	–	–	–	–	–
Skw D_2	–	–	–	–	–	–	–	–	.008	–	–	–	–	–	–	–	–
Skw D_3	–	–	–	–	–	–	.03	–	.009	–	–	–	–	–	–	–	–
Skw D_4	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Skw D_5	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Kurt D_2	–	–	.019	–	.029	.03	–	–	–	–	–	–	–	–	–	.016	.022
Kurt D_3	–	–	–	.04	–	–	–	–	–	–	–	–	–	–	–	–	–
Kurt D_4	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Kurt D_5	–	–	–	–	–	–	–	–	–	–	–	.04	–	–	–	–	–

significant results after False Discover Rate adjustment for such a large number of tests.

Decision Tree Analysis Results

We applied decision tree analysis to determine the most dominant and reliable discriminating extracted features of AD patients. We applied the three split criteria described in section "Subject Classification Using Decision Tree Analysis of Extracted Features" to the features extracted using the five wavelet functions, db2 through db10. The procedure provided 15 decision trees, many of which were different. We then selected the best decision tree based on the statistical significance of the selected features and minimal rate of false classification.

Resting Conditions

Initially, we applied the decision tree algorithms to the features extracted in the resting conditions (EC1–EO8) blocks of data using each of the five wavelet functions. The best decision tree was the one derived through Twoing index applied to the features obtained by db10 wavelet function. The algorithm identified the mean power of D_4 ($\sim\theta$) of the second EO state (EO4), as the first and most dominant discriminating feature of AD patients in resting states. These results indicate that if the mean power of D_4 in resting EO state of a subject is greater than 235.32, then that subject is identified as an AD patient, as shown in Fig. 5. The feature was determined to be statistically significant by both univariate and multivariate ANOVA. However, three subjects were misclassified. Note that, we did have decision trees with no false classification. However, none of the utilized features were statistically significant from a univariate perspective.

Cognitive and Sensory Tasks

Next, we applied the decision tree algorithm to the ensemble of active state recordings. The best decision tree was derived through Twoing index but when applied to the features obtained by db4 wavelet function. According to these results, the majority of AD patients exhibited increased minimum D_3 ($\sim\alpha$) values during auditory stimulation at 18 Hz combined with increased kurtosis of D_5 ($\sim\delta_u$) during PASAT with $\Delta t = 2$ s interval. While the remaining few exhibited decreased minimum D_3 values during auditory stimulation at 18 Hz combined with increased skewness D_5 (~2–4 Hz) skewness during PASAT with $\Delta t = 2.4$ s interval, as shown in Fig. 6. These results indicate that if the minimum value of D_3 during AS3 recording of a subject is greater than -72.15 and kurtosis of D_5 during P2.4 recording is great than 15.88, then that subject is identified as an AD patient. In addition, if the minimum value of D_3 during AS3 recording of a subject is less than -72.15 and skewness of D_5 during P2.0 recording is greater than 0.217, then that subject

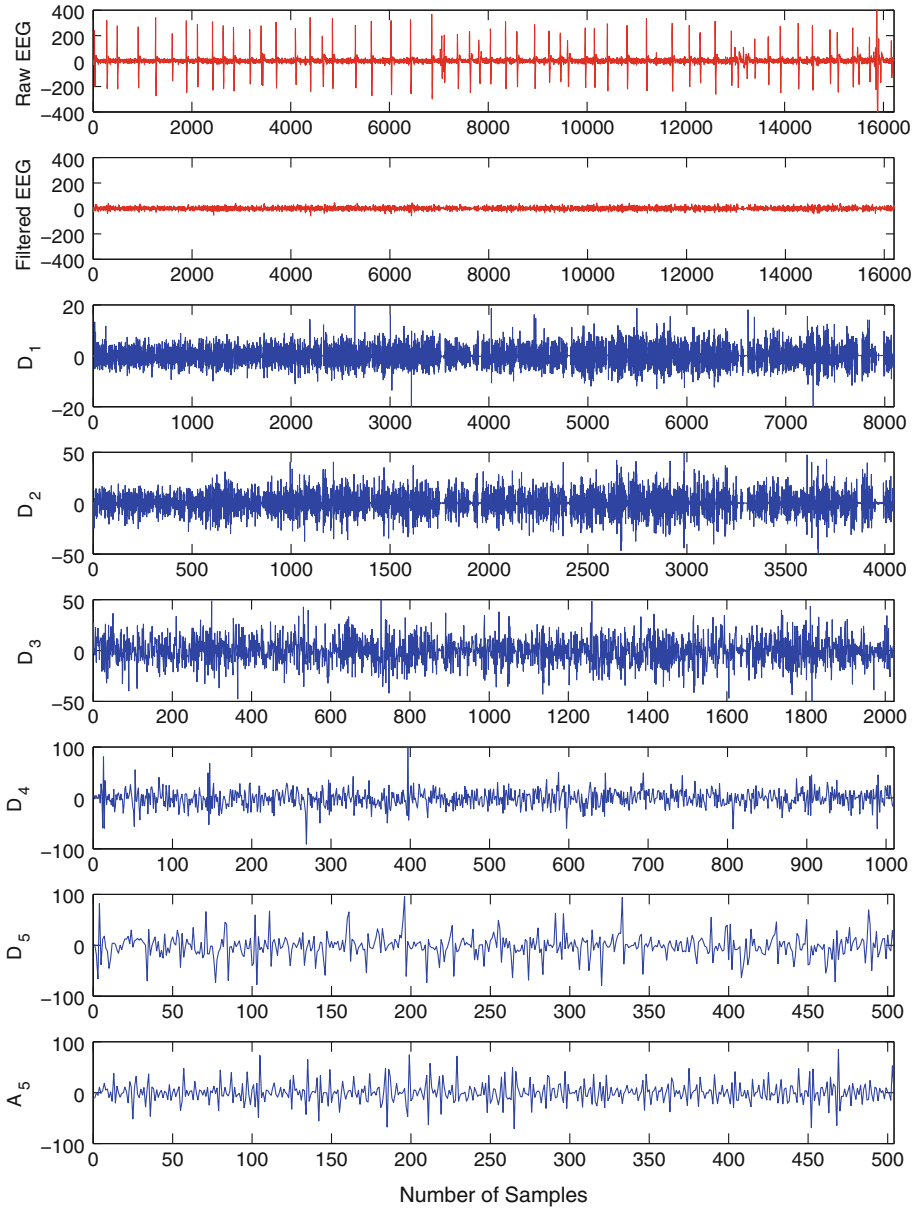

FIGURE 3. EEG signal and its DWT decompositions for CTL subject 5, EO4 block.

is identified as an AD patient. In this case, there were no false classifications and the first feature (min D_3) was found to be statistically significant by both univariate and multivariate ANOVA. D_5 kurtosis feature was also found to be statistically significant by univariate ANOVA. D_5 skewness feature, however, was not statistically significant from either univariate or multivariate ANOVA.

All Features

Combining the extracted features from all recording tasks, we applied the decision tree algorithm to all features. In this case a combination of features used in the first two decision trees were used to form the optimal tree, as shown in Fig. 7. Again, the Twoing index applied to the features extracted by db4 yielded the best decision tree. The majority of AD patients were identified in exactly the same way as the active state analysis. While the remaining few exhibited decreased minimum D_3 during auditory stimulation at 18 Hz combined with increased D_4 (4–8 Hz) mean power during resting EO state. These results again indicate that if the minimum value of D_3 during AS3 recording of a subject is greater than -72.15 and kurtosis of D_5 during P2.4 recording is great than 15.88, then that subject is identified as an AD patient. However, if the minimum value of D_3 during AS3 recording of a subject

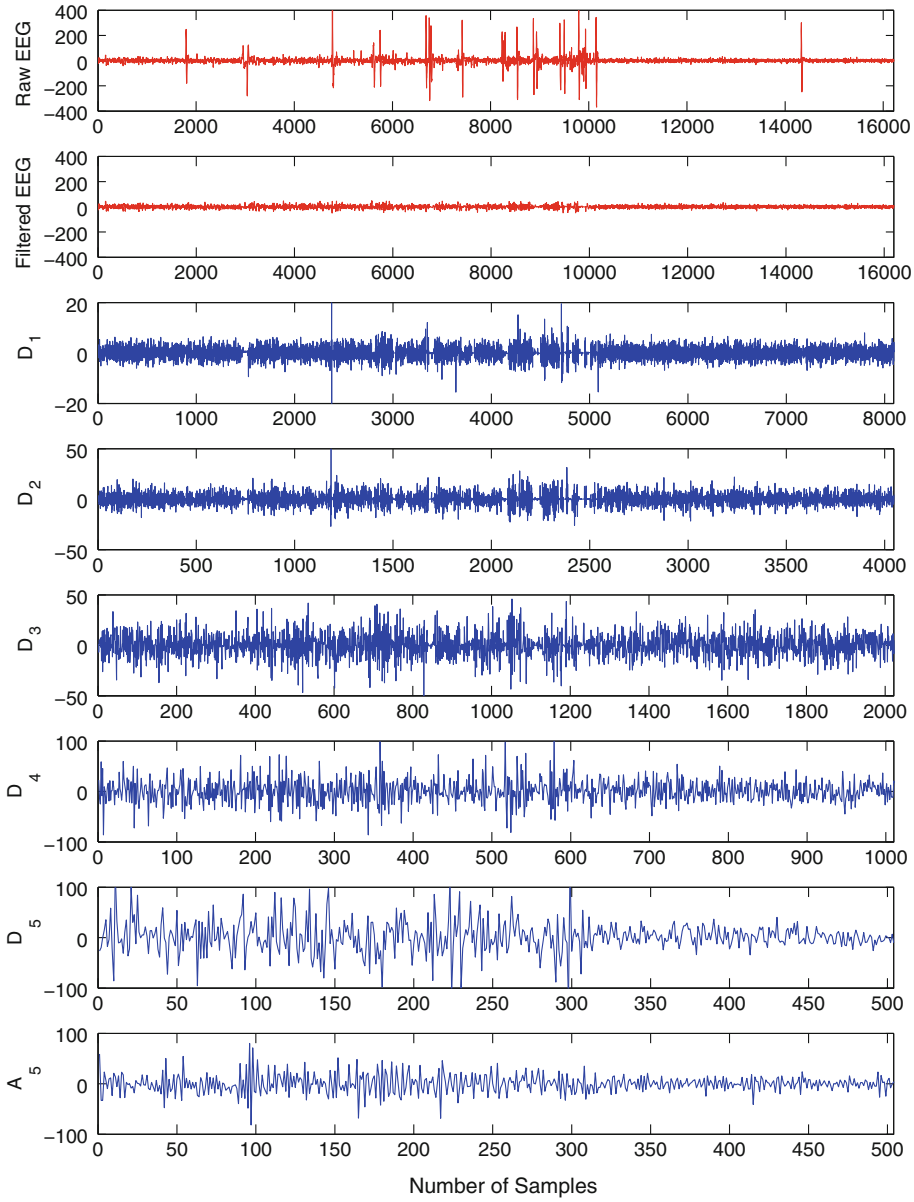

FIGURE 4. EEG signal and its DWT decompositions for AD subject 25, EO4 block.

is less than −72.15 and the mean power of D_4 during EO2 recording is great than 653.2, then that subject is again identified as an AD patient. Again, there were no false classifications and two features were found to be statistically significant by both univariate and multivariate ANOVA. However, D_4 mean power during resting EO state was only found to be statistically significant during the second EO state (EO4).

Internal Cross Validation

We randomly left one test subject out and reapplied the decision tree algorithms to all features of the remaining subjects as the training set. The best decision tree was determined to be exactly the same as the one shown in Fig. 7. As we changed the test subject, the mean power of D_4 during EO feature was replaced by another D_4 feature during EO in some cases. However, these features are not independent since we could not reject the hypothesis that the two multivariate means lie on the same line; i.e., the features are highly correlated. Furthermore, there were no false classifications when we applied the optimal decision tree classification to the randomly selected control subject.

DISCUSSION

Although the device used in this study is simple in design and only records one active channel of EEG

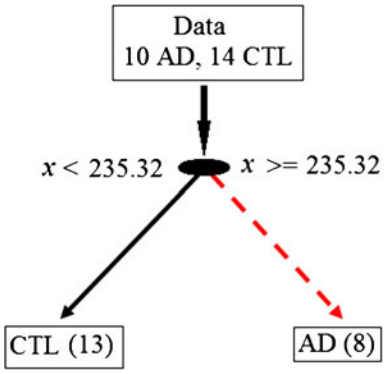

FIGURE 5. Optimal Decision tree for resting conditions. x is the mean power of D_4 of the second EO state (EO4). x is also a statistically significant feature of AD patients. The values within parentheses indicate the number of classified subjects.

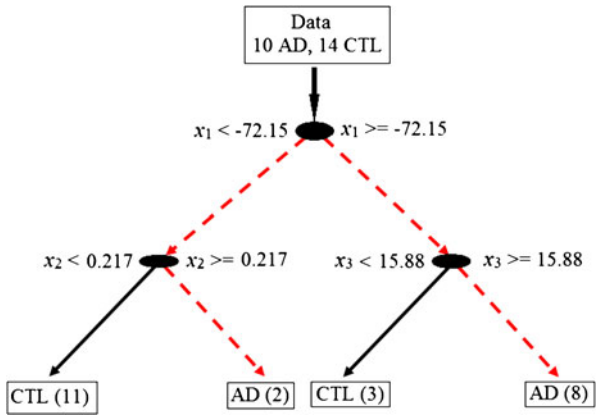

FIGURE 6. Optimal decision tree result for active states. x_1 is the minimum value of D_3 of auditory stimulation at 18 Hz (AS3), x_2 is the skewness of D_5 of PASAT 2.4 s interval (P2.4), and x_3 is the kurtosis of D_5 of PASAT 2.0 s interval (P2.0). Only x_1 and x_3 are statistically significant. The values within parentheses indicate the number of classified subjects.

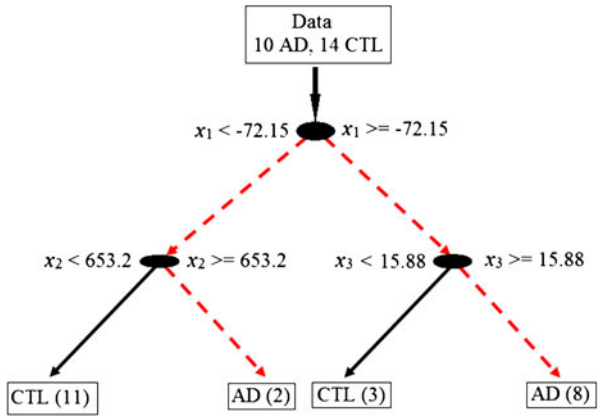

FIGURE 7. Optimal decision tree result using all recording blocks. x_1 is the minimum value of D_3 of auditory stimulation at 18 Hz (AS3), x_2 is the mean power of D_4 of the first EO state (EO2), and x_3 is the kurtosis of D_5 of PASAT 2.0 s interval (P2.0). Only x_1 and x_3 are statistically significant. The values within parentheses indicate the number of classified subjects. The values within parentheses indicate the number of classified subjects.

activity, it can accurately capture the spectral composition of the EEG signal between 2 and 30 Hz. The technical and analytical performance characteristics of the device are comparable to much more sophisticated clinical units as demonstrated not only by the excellent frequency and amplitude response as well as favorable signal to noise ratio. When compared to a single channel of a traditional clinical EEG equipment, its prominent features were indistinguishable. Most importantly, when traces were recorded, analyzed and then compared between resting EC and resting EO conditions, the single lead wireless device faithfully detected increased α rhythm activity as expected, with roughly seven to ten-fold elevation in the EC/EO power ratio. The main disadvantages of a single sensor device are its inability to perform multi-lead analysis such as coherence analysis, the inability to spatially map brain wave activity, such as seizure foci, and weakness in picking up potentials on the opposite side of the brain from the sensor perspective. There are, however, significant advantages including a meaningful increase in comfort and convenience for the patient, a faster more accessible portable technology that can move to the point of care, as well as a more affordable procedure leading to wider patient participation and neuro-diagnostic information earlier in the diagnostic algorithm. Of the EEG abnormalities reported in the literature,[21] it appears from our small sampled pilot study that slowing and decreased complexity of EEG in AD patients can be nonetheless captured with a single Fp1 sensor.

Once the analytical and clinical validity of the signals recorded by the device was established, we used a DWT with five different mother wavelets to extract candidate discriminating EEG features of AD patients. Single electrode EEG recordings at Fp1 during both resting and active states by AD and CTL subjects were analyzed. Given that AD is frequently characterized by progressive impairment in cognition and memory, the underlying hypothesis is that the addition of EEG traces recorded during the activated states will help identify clearer discriminating features with greater clinical performance as measured by sensitivity, specificity, and positive and negative predictive values. Extracted DWT statistical features from 5 level of decomposition were computed and compared between the AD and CTL groups. Statistical features of the DWT decomposition levels corresponding to the standard spectral brain frequency bands were used to identify numerous statistically significant features of AD patients in both resting and active states.

In the resting conditions, the mean powers of D_4 ($\sim\theta$) and D_5 ($\sim\delta_u$) were significantly higher for AD subjects compared to CTL subjects directly replicating the literature reported results of Wan *et al.*[33] Very importantly, our replication of this literature derived hypothesis supports the notion that a single lead device is able to replicate features observed with a clinical EEG system. Furthermore, the mean powers of D_2 ($\sim\beta$) were significantly lower for AD subjects compared to CTL subjects. These results are consistent with published literature where higher δ and θ activities and lower β activities have been reported for AD patients using other approaches.[21,23] Interestingly, we have observed in this small pilot study that the EO EEG recordings result in more discriminant features and are more dominant in identifying AD patients compared with the EC recordings. While, standard deviation, skewness, and kurtosis at several decomposition levels were also found to be statistically significant, we could not establish their independence through multivariate ANOVA.

Many of the EEG features of AD patients recorded during active state tasks were very different than those of resting conditions. D_3 ($\sim\alpha$) mean power, minimum, maximum, and SD during auditory stimulation at 18 Hz, were all significantly lower (magnitude) for AD patients when compared to control subjects. Multivariate analysis confirmed the univariate ANOVA results for these features. However the features were highly correlated since we could not reject the hypothesis that the features lie on the same line. Other significant discriminating features of AD patients in active states included skewness of D_2 and D_3 during the One Card Learning cognitive task, skewness of D_3 during Attention task, and kurtosis of D_5 during PASAT with 2.0 s interval.

A decision tree approach was used to identify the most predictive EEG features of AD patients. Since we used five different wavelet functions and three different split criteria for the decision trees, several unique classifications were obtained. In each case, we selected the best classification based on the statistical significance of the utilized features and the minimal rate of false classifications.

Classification of discriminating DWT extracted EEG features of AD patients utilized features from both active and resting states. In particular EEG features extracted during auditory stimulation, PASAT, and EO recording blocks were most useful and dominant. Overall, these findings suggest that although EEG recordings during resting conditions may be used to differentiate AD from control subjects, EEG activity during active engagement in cognitive and sensory tasks appear to provide additional and differential information, which in some cases were observed to be among the most discriminatory features of the AD subjects.

Although EEG recordings during performance of several different cognitive and sensory tasks provided a smaller number of features that were significantly different after univariate analysis between AD and CTL subjects, many unique features were nonetheless identified. The lack of statistical power in active states may be due to inter-subject variability in both EEG recordings and the ability of individual subjects to perform these tasks. Furthermore, in this study the sample size in each group was small compared to other studies[33] and as such likely contributed to low statistical power. Nonetheless, we found a few specific statistically significant discriminators that may lend themselves better to within subject analysis. Furthermore, some of the unique features derived through the analysis of active state recordings were used as dominant features in identifying AD patients through decision tree classification. Therefore, it is encouraging that even with such small sample size, novel features can be identified that differentiate AD and CTL groups.

It is important to note that this study is of an exploratory nature where a large number of statistical tests were conducted where multiple comparison corrections are too conservative and not strictly required.[6,27] We believe that the replication of the widely reported and accepted resting state EEG mean power features of AD provides a significant level of confidence in our results. However, we also note that our results do not provide rigorous evidence for each of the identified discriminating features and further studies to replicate these findings are still required to both verify and then validate any putative markers as predefined hypotheses.

In general, the initial results of this Alzheimer's diagnostic pilot study indicated that DWT analysis of EEG signal from a single electrode during an ensemble of resting and active brain states is potentially effective in identifying new discriminant features of patients with AD. However, we cannot be certain that the identified discriminating features and decision tree classifications are in fact due to AD and not inter-subject variability. We believe further studies with recordings from the same location as well as other locations on the scalp can help confirm our preliminary results and lead to further coherence analysis. In particular, when applied in the future to a larger sample size and recordings from other possible locations, we believe that the method can aid in the early diagnosis of AD.

We believe that our approach to identify features during active performance of cognitive tasks may play a more critical role in identifying AD in individual

subjects and early diagnosis. Longitudinal studies of AD patients and CTL may also be useful in showing normal rates vs. accelerated rates of change in the AD patients. Such studies may particularly be useful for patients with MCI as a means of tracking their progression to AD. Cognitive testing for minimally impaired subjects may also form an important baseline that should be followed over time to aid in the early diagnosis of AD.

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