Early Detection of Alzheimer's Disease using Non-Linear Analysis of Electroencephalogram (EEG) by Artificial Neural Network (ANN)

Sweta Soni[1]*, Shikha Mathur[2], Manu Saini[3]
***Corresponding Author**: Sweta Soni
*[1]Assistant Professor, Department of Physiology, Mahatma Gandhi Medical College & Hospital, Jaipur (Rajasthan), India,
Email : swetasoni926@gmail.com
[2]Associate Professor, Department of Physiology, Mahatma Gandhi Medical College & Hospital, Jaipur (Rajasthan), India.
[3]Assistant Professor, Department of Physiology, Mahatma Gandhi Medical College & Hospital, Jaipur (Rajasthan), India.

Abstract: -

The aim of present Electroencephalography (EEG) study was to investigate the role of non-linear analysis via Artificial Neural Network (ANN) for early detection of Amnesic Alzheimer's disease patient and normal elderly subjects. Katz's Fractal Dimension (FD) analysis was carried out from the EEG data of the samples (20 patients with Alzheimer's disease and 20 healthy controls) for the EEG manoeuvres (Eye closed, Eye open, hyperventilation, Memory task). EEG was recorded at rest and Mini Mental State Examination (MMSE) was performed before EEG recording in patients with Alzheimer's disease patient and normal elderly subjects. The EEG bands so evaluated were delta (0.2-3.9 Hz), theta (4.0-7.9 Hz), alpha (8.1- 12.9 Hz), beta (13.0 -30.0 Hz) and gamma (30.1-80 Hz). A significant decrease MMSE score was observed in patients when compared to controls (p=0.000). In the present study Artificial Neural Network (ANN) classifier was used for the diagnosis task. It has been observed that the highest classification accuracy was achieved as 97.94% (trained data set) in eye closed EEG maneuvers in Katz's Fractal Dimension (FD) in the present study. These results suggest that ANN classifier can detect Amnesic Alzheimer's patients from normal elderly subjects.

Key words: Amnesic Alzheimer's patients, Electroencephalography (EEG), Mini Mental State Examination (MMSE), Artificial Neural Network (ANN), Katz's Fractal Dimension (FD).

DOI Number: 10.14704/nq.2022.20.9.NQ44461 **Neuro Quantology 2022; 20(9):4031-4038**

INTRODUCTION:-

The German Physician, Alois Alzheimer (in 1906) was the first to profile and define the clinical entity of Alzheimer's disease as a form of dementia way. Clinically diagnosed Alzheimer's disease, alone or in combination with other illness, accounts for up to 90% of reported dementia cases in the west (Lim et al, 1999). The pathophysiology of Alzheimer's disease has been hypothesized and documented to be dysfunction of synaptic mechanisms with loss of functional neuronal pools. The features of Alzheimer disease are progressive deficits in memory and other aspects of cognition. Due to the deficits, patients with Alzheimer disease are unable to perform their daily course, leading to total dependence on their caregivers (Myron and Lipton, 2009). The deficits in memory result from synaptic dysfunction and neuronal loss. The DSM-IV-TR (American Psychiatric Association 2000) has laid down criteria for diagnosis of Alzheimer's disease which include impairment in **memory, orientation, language, visual processing, executive function and praxis**. Memory dysfunction is the first symptom which is recognized in Alzheimer's disease. It is detectable by neuropsychological tests in preclinical phases of the disease (Jacob et al, 1995). The typical memory impairment at onset involves difficulties with learning new information with relative preservation of remote information. Persons with memory loss initially present with the inability to remember recent events. In later stages, memory dysfunction extend to complete failure of recall for previously well remembered information, such as the names of a patient's own spouse and children (Myron and Lipton, 2009). The varied symptom – complex that delineates patients of Alzheimer's include unawareness of deficits, apathy, psychosis, mood disorder, agitation and sundowning (Myron and Lipton, 2009). The MMSE (Folstein et al, 1975) is used as a questionnaire - based tool that is employed to evaluate the cognitive profile of a subject/patient in clinical practice and helps in the determination of severity of dementia. The MMSE evaluates an individual's ability to orient with respect to space – time assessing a person's ability to associate and correlate the present with past experiences. The human mind is working along the principles of stochastic chaos that carve a trajectory around an attractor along the neuronal phase – space with a baseline noise profile per se and convey information packaged into coded neural impulses along the coordinates of space time differing from the coordinates of baseline noise in situations of attention and memory formation. This neuronal representation (information) of the impulses carried along the respective tract/pathway is then transformed and translated into the basic neural architectonics (physiological framework) of the human mind, i.e., **Memory**. **Short-term memory**, known as "primary" or "active" memory, is the part of memory which stores a limited amount of information for a limited amount of time (roughly 15-30 seconds). **Working memory** is the ability of storing and manipulating information for only a short period of time, if not rehearsed will be lost in 20 second or so (Engle, 2002). Working memory comprises both executive attention and memory process (Engle, 2002). Prefrontal cortex appears to play a fundamental role in short-term and working memory. Alzheimer's Disease (AD) is characterized by cognitive and intellectual deficits and behavior disturbance and is considered as the most common neurodegenerative disorder. The EEG has been used as a tool for diagnosing AD for several decades. EEG provides insight about neuronal functioning and seemingly represents the functioning of the human mind in real-time by representing the summated and synthesised electrical signals originating from various regions of the brain. EEG of a patient with Alzheimer's disease shows a distinct decrease in alpha and beta waves as well as an increase in delta and theta waves suggestive of a regression in evolution reverting to initial stage of lifeline in an attempt to overcome the basic dysfunction so caused by deposition of the pathognomic amyloid plaque and neurofibrillary tangles. EEG serves as an important tool for analyzing and diagnosing Alzheimer's disease by measuring brain wave pattern and the overall activity of the brain that helps in staging Alzheimer's disease (Estrada and Sote, 2009). Severity and progression of dementia is characterized by slowing of the EEG rhythms (Schreiter-Gasser et al, 1994; Nobili et al, 1999; Ihl et al, 1996). The findings so documented exemplify a trending towards low frequency range of electrical activity of respective neuronal pools spread across various designate cortical regions and is a reflection of the disease process that tends to retrogress in terms of the frequency pattern observed across the defined cortical areas echoing regression in growth and development. The Human Brain is the morphological and anatomical structural precept of the Central Nervous System that in essence serves the role of a supporting and regulatory organ system. The Human Mind is the Neurophysiological concept working across boundaries and domains of Human Brain adhering to Chaotic Dynamics. The Human Mind functions across space – phase of structural concept of Human Brain working along the strange attractor trajectory sub serving a particular function in characteristic real time. The underlying principles of neuronal dynamics follow the stipulations so laid down by the phenomenon of chaos. *Chaos Theory* represents a loosely related body of concepts, including sensitive dependence on initial conditions, bifurcation, self-organization, fractals, and strange attractors, that seek to describe the behavior of non – linear systems at higher levels of complexity, a premise that help expound both the chaotic and the organized features of complex systems (Stewart, 1989). Another interesting aspect of chaos is fractal geometry. Fractals were first created using computers to iterate a nonlinear equation, letting the internal sensitivity of the equation create shapes and figures on the screen. Polish mathematician Mandlebrot (1977) coined the name fractal to describe the fragmented, irregular nature of these images. The EEG, one of the most complex biological signals, requires the use of new mathematical methods. Applying nonlinear dynamic analysis to the EEG has offered valuable information on cortical dynamics.

Nonlinear dynamical methods might provide a useful tool to help in understanding brain electrical activity in terms of the collective dynamics of neurons, as well as improvement of the accuracy of differential and early diagnosis of AD (Jeong, 2004). Several studies have showed the usefulness of nonlinear methods to analyze the EEG in patients with AD (Stam, 2005). Fractal dimension was introduced to detect AD by Besthorn (1997).

In this context the present study was undertaken to explore neural dynamics as patterned through EEG rhythm and to appreciate an insight into the functioning of human mind in relation to cognitive decline.

MATERIAL & METHOD: -

The study was conducted in the Department of Physiology in association with the Department of Neurology, S.M.S. Medical College, Jaipur and the Department of Neurosciences (Cognitive Function Section), Santokaba Durlabhji Memorial Hospital (SDMH), Jaipur. The study design was a hospital based observational case - control study. All experimental protocols had been approved by the Institutional Ethics Committee. Informed written consent was obtained from all the subjects and patients or their caregivers who were enrolled in the present study. Thirty healthy controls and twenty Amnesic Alzheimer's disease patients were recruited in the present study. The sample size so required was 30 in each group at 95% confidence interval and 80% power to verify the minimum expected difference of 1.9 (±2.2) in working memory task score between Amnesic Alzheimer's Disease Patient and Controls. Continuous data were summarized in form of mean and standard deviation (S.D.). The level of significance was kept at 95% for all statistical tests. The study group was recruited from the O.P.D. of Neurology, S.M.S. Medical College, Jaipur and the Department of Neurosciences (Cognitive Function Section), SDMH, Jaipur. The control group for study was composed of age and sex matched healthy controls from the Institute. All patients underwent history taking, physical and neurological examination, psychometric testing and neuroimaging procedures (magnetic resonance imaging, MRI with temporal lobe protocol of the brain) and laboratory testing to rule out other causes of cognitive impairment. All experimental protocols had been approved by the Institutional Ethics Committee. The study was carried out from August 2015 to January 2017. The inclusion criteria adopted for the present study were: patients between 55 – 75 yrs., complaint by the patient, or report by a relative 4033
or the general practitioner of memory or other cognitive disturbances; patients rated and categorized with the standardized diagnostic and severity instrument of MMSE. Patient with frontotemporal dementia, vascular dementia based on clinical and radiological grounds, extrapyramidal syndrome, psychiatric diseases, epilepsy, drug addiction, alcohol dependence, current or previous uncontrolled systemic diseases, traumatic brain injuries were excluded for the study.

EEG recordings

The EEG activity was recorded, continuously by using electrodes set in an elastic cap (Electro - Cap International,) and positioned according to the 10–20 international system (Fp1, Fp2, Fz, F3, F4, F7, F8, Cz, C3, C4, T3, T4, T5, T6, Pz, P3, P4, Oz, O1, O2). Impedance was kept below 5 Ω and electrical activities, amplified with a band-pass filter of 0.5 - 30.0 Hz, were digitized at sampling rate 256 Hz. Recording of EEG was taken in a sound attenuated, dimly lit room. The patients were instructed to stay sit with closed eyes and relaxed and were awake during the procedure of basal and specialized manoeuvres EEG - test run. The EEG bands we use so evaluated were delta (0.2-3.9 Hz), theta (4.0-7.9 Hz), alpha (8.1- 12.9 Hz), beta (13.0 -30.0 Hz) and gamma (30.1-80 Hz). QEEG was done for all the patients and controls using BESS (brain electro scan software) of the Axxonet System (India). Artefact free epochs were chosen because after every of 2-3 seconds the changes both inclusive and exclusive in the amplitude were taking place more than 10% and their spectral content evaluated by means of Fast Fourier Transform analysis.

Working Memory Task

After recording in the rest condition the working memory task was performed. Patients were instructed to hear word list carefully and were asked to repeat the word list during which time – course the EEG was recorded with eyes closed. LB-Memory Test is based on the computerised administration of standardised sequentially ordered, auditory, verbal, free recall tasks. The method describes organizational processes underlying memory search and retrieval. Specifically, it adopts a decomposition technique to evaluate distinct contributions of list structure and context on different components of recall.

Memory tasks (named as: List A, List B, and List C) involve the sequential acquisition and immediate recall of 3-word lists. List A consists of 18 semantically unrelated items, whereas Lists B and C present 18 semantically related items, equally distributed across 3 different mutually-exclusive taxonomic categories, 6 items for each category. The automatic scoring system provides the profile of results for each subject.

The score of working memory performance was computed as the total number of correctly remembered words. It was ensured that at the time of EEG recording, the subject was not on any medication that influenced the EEG rhythm (LB – Memory test – 2009).

Artificial Neural network

In Artificial Neural Network (ANN), the burden of making assumptions about the structure of the data is transferred to the training of hidden layers that solve "sub-problems" of the given input. This allows us to find nonlinear relationship of features along and between channels that can offer greater predictive power than the earlier models discussed (Bhagavatula, 2010). We evaluated the performance on hidden 35 layers trained training and test performance. 85% of the trials were used for training and 15% of the trials were held out for testing neural network consisting 35 hidden layer's was trained on samples of epochs 50 for each 20 patient and 20 controls for each 3 seconds and the result were calculated on 85% training data and 15% for testing evolution.

Nonlinear Parameters

Katz's Fractal Dimension (FD) analysis was carried out from the EEG data of the samples (20 patient and 20 controls) for the EEG manoeuvres (Eye closed, Eye open, hyperventilation, Memory task.). 50 epochs were selected, and corresponding fractal dimensions were calculated for each class of EEG monomer for each patient and control.

Pre-processing of EEG Data: -

The cortically generated EEG is offer contaminated by several non-cerebral artifacts origins viz. eye blinks, ocular moments, random noise such as electrical disturbances, instrumentation noise external electromagnetic activity etc. To remove these artifacts EEG signal pre-processing is the most essential step prior to information extraction from EEGs. Pre-processing of EEG data enhances the usability of these signals in diagnosis task of the particular disease.

Feature Extraction: -

Feature extraction methodology is performed on the EEG record of 20 healthy controls and 20 AD patients for the data segment of 50 epochs each for 3 second. Total 1000 such events are considered in the present study for each class of EEG data i.e. AD healthy controls and patients with AD.

Katz's Fractal Dimension

The Value of FD $_{\text{Mandelbrot}}$ is governed by measurement units. Katz's combined a unit of measure of 'yardstick' definition with Mandelbrot's original work and figured out that to computer FD, discretization of space should be done (Katz's, 1988).

In order to reduce system complexity and computational cost, EEG activity registered through six EEG electrodes viz. FE, F4, C3, C4, P3, and P4.Artificial Neural Network (ANN) training and classification for disease diagnosis was carried out by Mat lab Neural Network tool version 2014.

Statistics

The Microsoft excel 2007 was used for statistically analysis of data. The unpaired t-test was used for the mean comparison of all parameters between patients with Alzheimer's disease and control subjects. With intention to avoid type 2 errors, we considered two – sided p values < 0.05 to be significant.

RESULTS AND DISCUSSION

Table 1: Demographic and clinical data of the Alzheimer's disease and control population

Demographic and clinical Variables		**Patient (N=20)**	**Control (N=30)**	**P value**
Gender	Male	11	21	0.281
	Female	9	9	0.281
Age	Mean	69.10	66.63	0.124
	SD	6.146	3.986	
MMSE Score	Mean	12.75	28.23	0.000*
	SD	3.573	1.194	

Table 2: Nonlinear parameter during eye close session of EEG in trained data set

Classifier performance /accuracy	**Katz Fractal Dimension**
Correct	97.94%
Incorrect	2.06%

EYE CLOSE KATZ TRAINED DATA

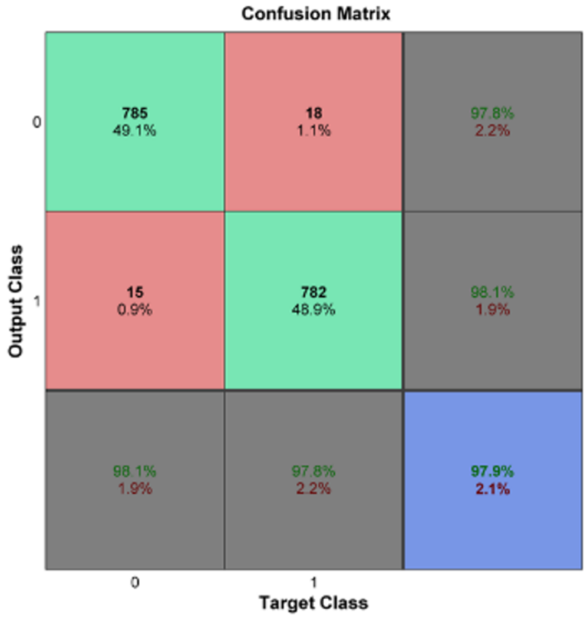


Table 3 : Nonlinear parameter during eye close session of EEG in tested data set

Classifier performance /accuracy	**Katz Fractal Dimension**
Correct	98.17%
Incorrect	1.83%

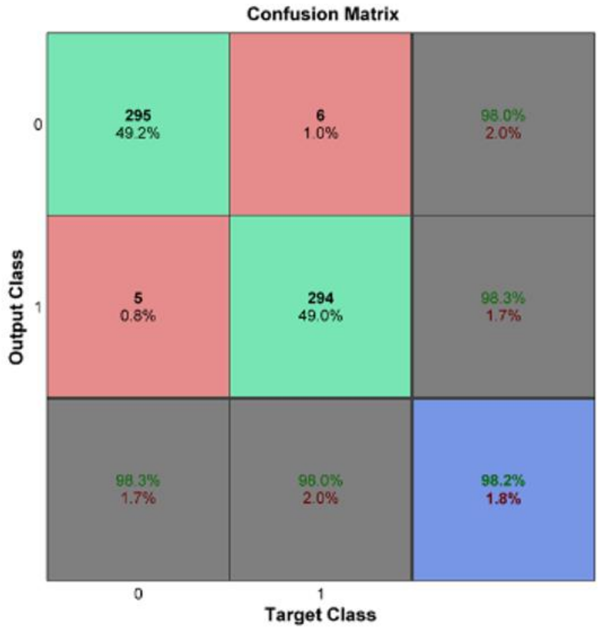


Table 4: Nonlinear parameter during eye open session of EEG in trained data set

Classifier performance /accuracy	**Katz Fractal Dimension**
Correct	97.56%
Incorrect	2.44%

EYE OPEN KATZ TRAINED DATA

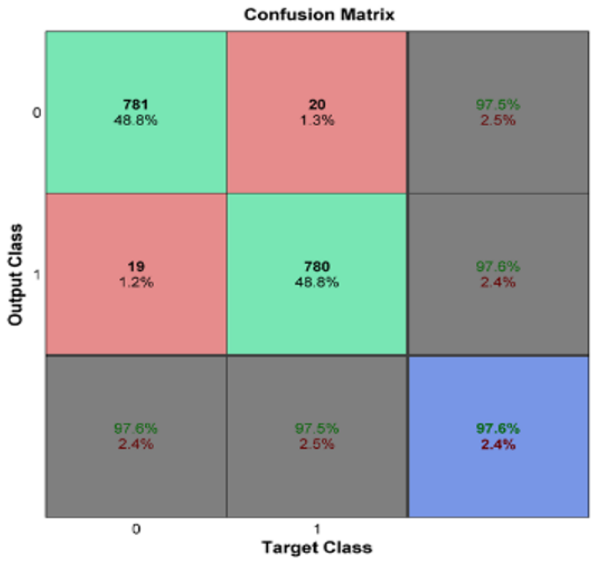


Table 5 : Nonlinear parameter during eye open session of EEG in tested data set

Classifier performance /accuracy	**Katz Fractal Dimension**
Correct	99.50%
Incorrect	0.50%

EYE OPEN KATZ TESTED DATA

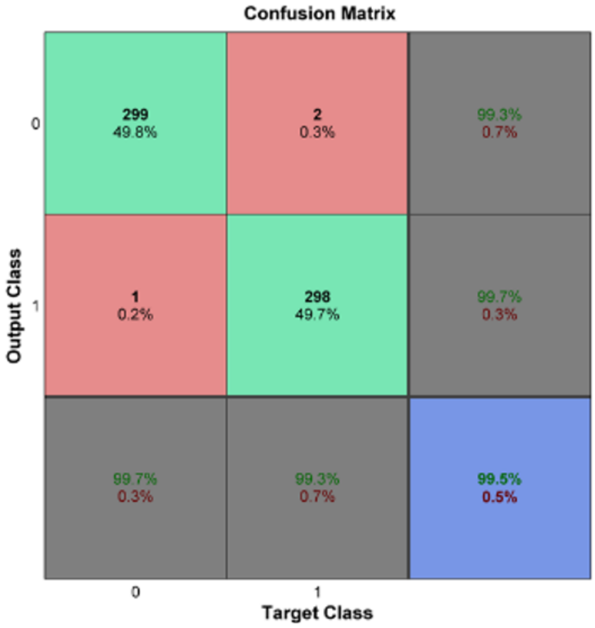


Table 6 : Nonlinear parameter during hyperventilation session of EEG in trained data set

Classifier performance /accuracy	Katz Fractal Dimension
Correct	95%
Incorrect	5%

HYPERVENTILATION KATZ TRAINED DATA

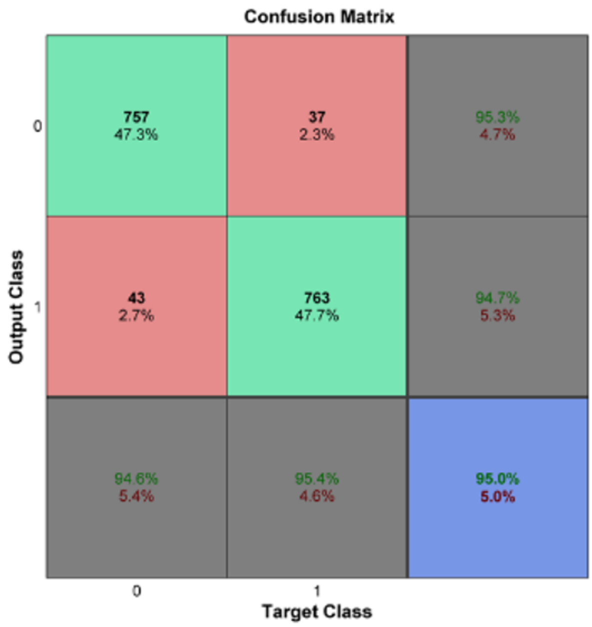


Table 7: Nonlinear parameter during hyperventilation session of EEG in tested data set

Classifier performance /accuracy	Katz Fractal Dimension
Correct	96.67%
Incorrect	3.33%

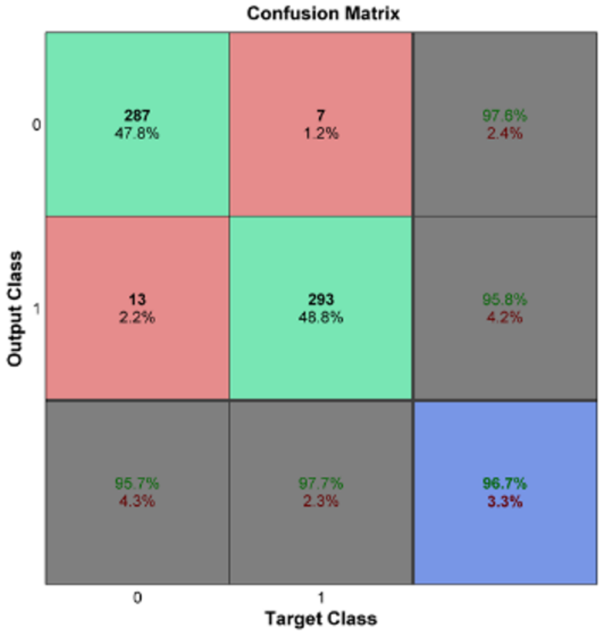


Table 8: Nonlinear parameter during working memory task session of EEG in trained data set

Classifier performanc e /accuracy	Katz Fractal Dimension
Correct	95.88%
Incorrect	4.12%

WORKING MEMORY TASK KATZ TRAINED DATA

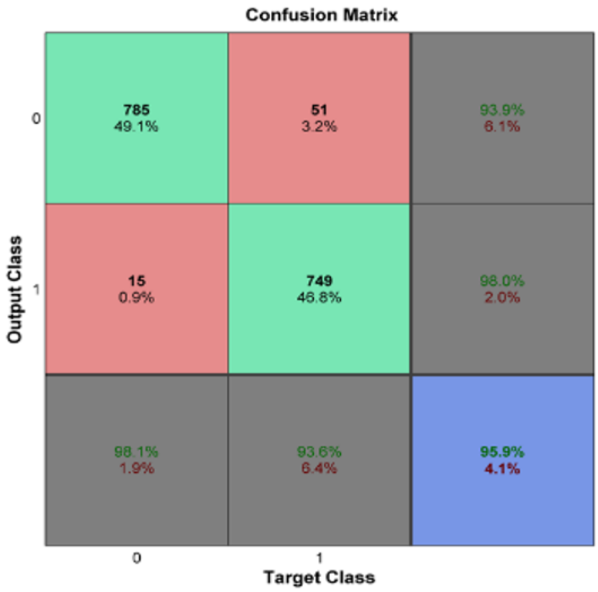
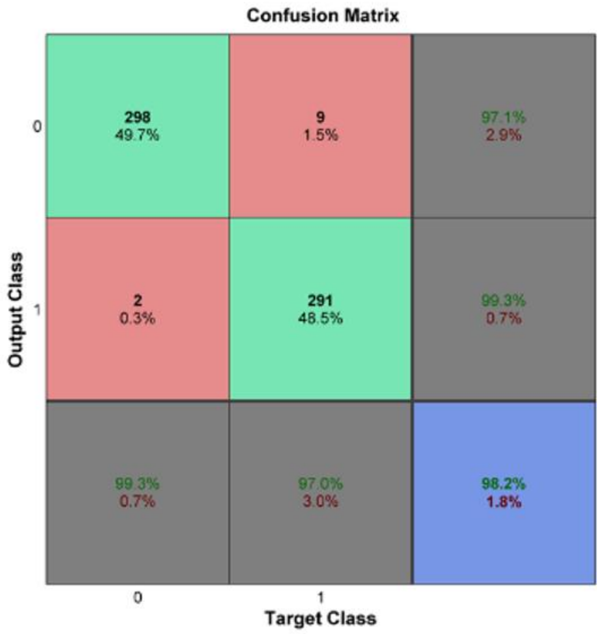


Table 9: Nonlinear parameter during working memory task session of EEG in tested data set

Classifier performa nce /accuracy	Katz Fractal Dimension
Correct	98.17%
Incorrect	1.83%



RESULTS OF NONLINEAR ANALYSIS

In order to diagnose Alzheimer's disease (AD) patient, the extracted features of EEG activity are given to the classifier algorithm for training and test performance. In the present study Artificial Neural Network (ANN) classifier was used for the diagnosis task. It has been observed that the highest classification accuracy was achieved as 97.94% (trained data set) in eye closed EEG maneuvers in Katz's Fractal Dimension (FD) in the present study (Table 2).

DISCUSSION

The Human Brain is the morphological and anatomical structural precept of the Central Nervous System that in essence serves the role of a supporting and regulatory organ system. The Human Mind is the Neurophysiological concept working across boundaries and domains of Human Brain adhering to Chaotic Dynamics. *Chaos Theory* deals with nonlinear things that are effectively impossible to predict or control, like turbulence, weather, the stock market, our brain states, and so on. These phenomena are often described by fractal mathematics, which captures the infinite complexity of nature. Many natural objects exhibit fractal properties, including landscapes, clouds, trees, organs, rivers etc., and many of the systems in which we live exhibit complex, chaotic behavior. Recognizing the chaotic, fractal nature of our world can give us new insight, power, and wisdom. In the present study a significant decreased MMSE score (p=0.000) was observed in patients suffering from AD as compared to age and sex matched healthy controls (Table 1). This finding as an observation, documented by Stam et al,(2003) who observed that low MMSE scores in AD patients also exhibit low beta band synchrony. They concluded that loss of beta band synchrony occurs early in mild AD patients and correlates with cognitive impairment. Hsiao et al, (2013) found that MMSE scores were strongly correlated with the magnitudes of spectral power at the theta and alpha bands in posterior portion of default brain network.

In the present study Artificial Neural Network (ANN) (a nonlinear feature extraction technique) was used and evaluated for early diagnosis of AD using EEG signals. Katz's Fractal Dimension (FD) was calculated from the recorded EEG activity and classified using ANN classifiers. It is observed from the results of the classification that the proposed technique successfully diagnosed the diseased patient using nonlinear feature of EEG signals. In the present study Katz's FD was found to be the most efficient feature in AD diagnosis task and the highest classification accuracy is obtained as 97.94% during eyes closed session in the present study.

EEG can have a good prognostic value in diagnosing the disease stages. Further nonlinear evaluation could give us a framework or opinion window in developing of algorithm that could be prognosis of disease.

Limitation of the present study:-

The sample size was small. Though algorithm so prepared and designed needs to be further tested and validated in the field for the conformation of final outcome and conclusion of the signature of disease processed that underscore and highlighted in the present study.

CONCLUSION: -

Artificial Neural Network (ANN) classifiers technique successfully diagnosed the diseased patient using nonlinear features of EEG signals. In the present study Katz's Fractal Dimension (FD) was found to be the most efficient feature in AD diagnosis task and the highest classification accuracy is obtained as 97.94% during eye close session. The present study was undertaken to process the EEG data further digitally and on principles of nonlinear chaotic dynamics in order to elicit deciphers and decode the cryptic or hidden signature of the disease process of Alzheimer's disease. Moreover when the EEG time series subjected to Fast Fourier Transform interesting and perceptible changes were observed and documented that could be appreciated in the EEG waveform. The present study opens new eve news and horizons in the management of AD wherein quantitative and digital EEG when process along the principle of nonlinear chaotic dynamics could serve as a potential tool as an important diagnostic and prognostic that has a propensity to enumerate various features of Alzheimer's disease.

BIBLIOGRAPHY:-

Besthorn C., Zerfass R., Geiger-Kabisch C., Sattel H., Daniel S., Schreiter- Gasser U., Forstl H., 1997. Discrimination of Alzheimer's disease and normal aging by EEG data. Electroencephalogr Clin Neurophysiol 103, 241-248.

Bhagavattula V., 2010. Advanced signal processing and machine learning approaches for EEG analysis.

Engle R.W., 2002. Working Memory Capacity as Executive Attention. Current Directions in Psychological Science. American Psychological Society Feb 11(1), 19-23.

Estrada L., Soto C., 2009. Current Hypotheses and Research Milestones in Alzheimer's Disease. 7, 217-226.

Folstein M.F., Folstein S.E., McHugh P.R., 1975. "Mini-mental state": a practical method of grading cognitive state of patients for the clinicians. J Psychiatr Res 12, 189-198.

Hsiao F.J., Wang Y.J., Yan S.H., Chen W.T., Lin Y.Y., 2013. Altered oscillation and synchronization of default-mode network activity in mild Alzheimer's disease compared to mild cognitive impairment: an electrophysiological study. PLoS ONE 8 (7), article e68792.

Ihl R., Dierks T., Martin E.M., Frolich L., Maurer K., 1996. Topography of the maximun of the amplitude of EEG frequency in dementia of the Alzheimer type. Biol Psychiatry 39, 319-25.

Jacobs D.M., Sano M., Dooneief G., 1995. Neuropsychological detection and characterisation of preclinical Alzheimer's disease. Neurology 45, 957-962.

Jeong J., 2004. EEG Dynamics in patients with Alzheimer's disease. Clinical Neurophysiology 115, 1490–1505.

Katz M., 1988. Fractals and the analysis of wavwforms. Comput Biol Med, 18(3), 145-156.

LB-Memory Test Manual-draft version. October 2009.

Lim A., Tsuang D., Kukull W., 1999. Clinico-neuropathological correlation of Alzheimer's disease in a community-based case series. J Am Geriatr Soc 47, 564-569.

Mandelbrot B. B., 1977. Fractals: Form, chance, and dimensions. San Francisco: W. H. Freeman.

Myron F., Lipton M., 2009. The American Psychiatric Publishing Textbook of Alzheimer Disease and Other Dementia, First Edition, 2009. Neural Comput. 1998 May 15, 10(4), 821-835.

Nobili F., Copello F., Vitali P., Prastaro T., Carozzo S., Perego G., Rodriguez G., 1999. Timing of disease progression by quantitative EEG in Alzheimer's patients. J Clin Neurophysiol 16(6), 566-73.

Schreiter-Gasser U., Gasser T., Ziegler P., 1994. Quantitative EEG analysis in early onset Alzheimer's disease: correlations with severity, clinical charac- teristics, visual EEG and CCT. Electroencephalogr Clin Neurophysiology 90, 267-272.

Stam C., 2005. Nonlinear dynamical analysis of EEG and MEG: Review of an emerging field. Clinical Neurophysiology 116, 2266 – 2301.

Stam C.J., van der Made Y., Pijnenburg Y.A., Scheltens P., 2003. EEG synchronization in mild cognitive impairment and Alzheimer's disease. Acta Neurol Scand. Aug 108(2), 90-96.

Stewart I., 1989. Does God play dice? The mathematics of chaos. Middlesex, MA: Penguin Books.

eISSN 1303-5150 www.neuroquantology.com