A Study on Alzheimer's Disease

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ABSTRACT
Alzheimer's disease is prolonged neurologically degraded disease which gets exaggerated with the course of time. While in its progression, Alzheimer's disease gives rise to memory shortfall and cognitive fall off. It is a constituent of two pathological conditions i.e. Neurofibrillary tangles, which the clusters formed by hyperphosphorylation of microtubule related protein are called Tau, and Senile plaque which contains β-Amyloid, a neurotoxin, which causes impairment of synaptic plasticity and may also change the functionality of many ionic channels. These two deadly proteins are the sure signs of Alzheimer's disease and attack the Hippocampus region thereby starts damaging the hippocampal pyramidal neurons in its early stage.

According to the survey on Alzheimer's disease, it is the 6th main cause of deaths in US and in upcoming years, this will become the 3rd main cause of deaths. But, despite researches, therapies and awareness, the actual cause of Alzheimer's disease is still a big question mark. "What is the actual cause of it"? "When and how it gets accumulated on a neuron"? "How a person can know if he is infected with this disease"? These are some of the questions that are yet to be answered.

In this paper, a detailed overview of the work done till now for the identification and treatment of Alzheimer's disease is presented.

Keywords
Alzheimer's disease, neurofibrillary tangles, β-amyloid, tau protein

1. INTRODUCTION
Alzheimer's disease (AD) is a prolonged neurologically-deteriorated disease which is analogous to memory shortfall and cognitive fall off. Alzheimer's disease is classified by two neuro-pathological constitutions: neurofibrillary tangles (NFTs) and senile plaques (tau) [16].

Neurofibrillary tangles (NFTs) are said to be the primary cause of Alzheimer's disease. NFTs are clusters which are formed by hyperphosphorylation of microtubule related protein called a Tau. This protein gets aggregated in an insoluble form.

Another neuro-pathological constitution responsible for Alzheimer's disease is senile plaques which contains β-Amyloid (Aβ), a neurotoxin that causes neuronal dysfunction and death of cells [17]. β-amyloid also impairs the synaptic plasticity (the potential of synapses to change its behavior according to the activity performed) [18]. This harmful protein may also change the functioning of ionic conducting channels, for ex. A-type fast-inactivating K+ channels (I_A), and delayed rectifier K+ channels (I_K)[1], L-type Ca2+ channels (I_{Ca})[2].The β-amyloid peptide affects the Hippocampal pyramidal neurons in the early stage and later take over the entire neuron thereby blocking A-type K+ currents in Hippocampal neurons and inflates neuronal excitability [7, 19]. For a healthy neuron the threshold value of membrane conductance is -55mV, i.e. below -55mV, neuron will not fire the signal but as soon as membrane conductance reaches the required threshold value, an action potential is generated in the form of a spike. When excitability of the neuron gets inflated, the threshold value for that neuron changes, or rather increases. Due to this increase in threshold value, the action potential for the neuron is not generated and hence it becomes unable to fire the signal received by it. Damaged Hippocampal may cause intense Amnesia.

As stated above, Alzheimer's disease is a progressive neurodegenerative disease and to predict its early detection is a difficult task to achieve. While a number of researches have been done and still are being done for the detection of Alzheimer's disease in its early stages, the process is still under progress because in huge population, it is very difficult to say the early stage of Alzheimer's disease. Researches are still going on for the detection of AD in the mild stage and its treatment in mild as well as in severe stage.

Below is a detailed overview for diagnosis and treatment of Alzheimer's disease in its mild to severe stage.

[1] **Good et al. 1996** proposed a whole cell voltage- clamp technique to measure synthetic β-amyloid in the hippocampal neuron of rat and before and after application of β-amyloid protein that caused a decrease in voltage in membrane conductance were also obtained. The voltage decrease in membrane conductance reflects that the accumulation of peptide over the axon affects the functionality of voltage gated channels and particularly blocks the fast- inactivating K+ currents. In this experiment, a decline in membrane conductance was viewed for 61% of neurons which were affected β-amyloid and in responding neurons, an average 45% decline in membrane conductance was observed. This shows that the accumulation of β-amyloid peptide in the neuron not only affects the functionality of that neuron only but its neighboring neurons also.

[2] **Webster et al. 2006** gave a study that elongated hypoxia critically up-regulates the useful expression of L-type Ca^{2+} ion channels in cerebeller granule neurons. The result of this prolonged selectivity is relying on the continuous creation of β-amyloid peptide. In central nervous system, the L-type Ca^{2+} ion channels play an important role in wide functionalities of brain including long term potentiation, mood and memory and many more. Therefore, the alterations caused by hypoxia in function expression of brain are likely to have far reaching effects.

[3] **Almadlou et al. 2010** proposed a wavelet approach for diagnosis of Alzheimer's disease based on EEG. The proposed approach employs the visibility graph (VG), one of the recent concepts of graph theory. The research

is based on the belief that non-linear traits may not show difference between Alzheimer's disease and control group, but may constitute identifiable distinctions in some sub-brands. Therefore, the complexity of EEG's is calculated using the visibility graph and sub-brands produced by wavelet decomposition. Furthermore, for the purpose of features selection, analysis of variations is used and on selected features, two classifiers are applied i.e. Radial Basis Function Neural Network (RBFNN) and two state classifier PCA+RBFNN, which will distinguish between Alzheimer's disease and control EEG's. Finally, the proposed approach is validated with 97.7% accuracy.

[4] **Takahashi et al. 2010** gave a study about the correlation of β-amyloid and tau protein in Alzheimer's disease. The two hallmarks of Alzheimer's disease i.e. Tau neurofibrillary tangles and β-amyloid are considered to be the best correlates of cognitive deterioration and loss of synapses. In this paper they have shown that tau and β-amyloid co-exists at synapses and creates a hindrance to the communication (transmission of signal) amongst neurons.

[5] **Colom et al. 2010** gave a study of how β-amyloid alters the septo-hippocampal anatomy and its functionality. The study indicates that cholinergic and glutamatergic septal neurons are more attackable by β-amyloid and glutamatergic connectivity is disabled by amyloid. This alteration in a number of septal neurons and their connectivity results in abnormal theta rhythms in hippocampal region.

[6] **Morse et al. 2010** proposed a computational model for hippocampal pyramidal neurons for analysis of bAPs dendrites under K+ ion channel block, because dendrites are indirectly but more vulnerable to inflated excitability. Therefore, dendrites are of more concern in this paper. From the prediction results, it can be said that in CA1 hippocampus, the early β-amyloid pathology could have most profound and early impact on the fine oblique dendrites of pyramidal cells because bAPs is presumed to play a key role in learning and memorization.

[7] **Li et al. 2011** proposed a longitudinal Voxel Based Morphometry method to plot the progression of Gray matter changes in Alzheimer's disease. At the initial stage, sMRI images are collected as a reference for the next stage. In the second stage (after one or two years), the MRI images of same patients are compared with the images kept for reference. A large number of patients (51 out of 64) were considered to be in early stage with CDR = 0.5 (for very mild stage). The hippocampal and MTG are the two key regions being considered. Finally, a causality analysis was carried out for the determination of pattern associated with the atrophy accumulation in hippocampal and MTG regions, resulting in an extensive loss of gray matter in these two regions. It means that the portion of the brain gets thin and results in excessive cognitive decline.

[8] **Zou et al. 2012** proposed a hippocampal-septal computational model which is based on the formalism of Hodgkin and Huxley model. The model comprises of three types of neurons i.e. pyramidal, OLM and basket neurons from hippocampus CA1 and MSGAB, a neuron from medial septum. In this paper, the influence of β-amyloid on hippocampal network dynamics is identified by estimating the changes in theta band power of hippocampo-septal.

[9] **Spies et al. 2013** proposed a prediction model which predicts that Dementia is a consequence of Alzheimer's disease. For the calculation of probability, the levels of CSF P-Tau and CSF AB42 are considered. To build the model, the dataset of more than 500 patients was used and validated with an independent and extensively large dataset. The model was also made flexible to the size of the dataset. The study also reveals that women are more affected by Alzheimer's disease than men. The advantage of this model is that if any critical information is to be included then it can be easily added without agitating the existing information. An overall accuracy of 91% has been obtained from this prediction model with the limitation that there were some misclassifications occurred.

[10] **Maia et al. 2014** proposed a theoretical computational model, which reflects how concussion and traumatic brain injury (TBI) may lead to compromised axonal functionality or Alzheimer's disease. In this paper, the axon, after TBI is investigated with different classes of spike trains and how potentially they can be misclassified. Depending upon the length of spike train and the firing rate, the information loss by the axon and the chances of misclassification can be analyzed.

[11] **Abuhassan et al. 2014** developed a compensating mechanism for synaptic loss in Alzheimer's disease. The proposed methodology is based on the Izhikevich model and two independent compensatory mechanisms were modeled i.e. global and local compensation mechanism. In addition to this, one more compensation mechanism was developed which was a combination of both global and local compensation mechanisms, working in parallel. The results show that therapeutics, if they are targeting compensation mechanism then if will be efficient for the treatment of Alzheimer's disease.

[12] **Grill et al. 2018** conducted an Alzheimer's disease prevention trial and interviewed 33 people in which there reactions were recorded about "not elevated" amyloid PET scan. Some of them were told that they had no plaque or amyloid and some of them were told that they did not signify sufficient elevated amyloid to qualify. The reactions to the results were different for every person. Some felt relief of not having amyloid plaque, while some were disappointed that they cannot participate in further process.

[13] **Dou et al. 2018** gave a network Meta analysis to extensively compare and line-up different types and dosages to boost the learning and thinking capability. In this study, some evidences were provided which shows that galantamine and donepezil may be given to patients for mild to moderate Alzheimer's disease and a combination of donepezil and memantine may be given to patients for moderate to severe Alzheimer's disease. However, it was also stated that dosage may differ from person to person and may not provide complete relief to AD patients or change their behavior. Medicine like rivastigmine may cause adverse effect, if taken in excess. Therefore, it can be said that some drugs have limitations associated with it rather than only benefits.

[14] **Baldeiras et al. 2019** proposed a tool to estimate the succession of Alzheimer's disease from mild cognitive impairment to dementia. The tool named "Erlangen score (ES)" is a useful tool which predicts the progression of dementia from Mild Cognitive Impairment (MCI) stage

and firmly depends on CSF biomarker trend. In this study, the patients are analyzed with different ES categories, covering four diagnostic groups. Patients with higher ES outcome are categorized in AD group and those with lower ES outcome are put in MCI-AD group. The results show that only 5% patients were misclassified a neurochemically unpredictable AD and one in 66 were misclassified as neurochemically predictable AD. The average accuracy of 98.5% was obtained.

[15] **Youm et al. 2008** proposed an AD Vaccine generated from transgenic tomatoes using Agrobecterium-mediated nuclear transformation. This vaccination was developed so as to prevent or delay the accumulation of β-amyloid.

Table 1: A succinct review of the related work is presented in below including different techniques used for diagnosis of Alzheimer's disease.

Paper	Year	Author (s)	Technique used	Result/ Conclusion	Research gaps
[1]	1996	Good et al.	Whole cell voltage clamp technique	Decline in membrane conductance was observed for about 61% of neurons and average of 45% for neighboring neurons.	The technique was applied to investigate the effect of amyloid peptide on fast-inactivating K^+ channel only. This technique may be a combination of this technique can be applied in some other ion channels to investigate the functionality after accumulation of amyloid peptide.
[2]	2006	Webster et al.	Consequences of prolonged hypoxia on L-type Ca^{2+} ion conducting channels.	The alteration caused by hypoxia in function expression is likely to get wide-ranging effects.	The experiment was done, considering only L-type channels. This study can also be extended to test the effect of prolonged hypoxia on other ion conducting channels.
[3]	2010	Almadlou et al.	Wavelet based approach on EEG	the proposed approach is validated with 97.7% accuracy	The complexity of visibility graph increases with increasing attributes, resulting in decrease in accuracy.
[4]	2010	Takahshi et al.	Co-occurrence of β-amyloid and Tau protein in AD	β-amyloid and Tau protein are considered to be best correlates of cognitive deterioration and loss of synapse.	This study only examines the co-occurrence of Aβ and Tau, but the relation between these two is yet to be examined for different sections of brain.
[5]	2010	Colom et al.	Alteration of septo-hippocampal anatomy by β-amyloid.	Alteration in a number of septal neurons and their connectivity results in abnormal theta rhythms in hippocampal region.	To carry a reduced amplitude theta slow firing rate must be increased.
[6]	2010	Morse et al.	Computational model for hippocampal pyramidal neuron.	Fine oblique dendrites are more vulnerable to inflated excitability.	The model incorporates changes in concentration of potassium in the septal region. It may

					be also applied to measure the change in calcium concentration with application of Aβ.
[7]	2011	Li et al.	Longitudinal Voxel Based Morphometry method.	The portion of the brain gets thin and results in excessive cognitive decline.	In this study, the causality model incorporated on linear effect and neglected the non-linear effects like age of patients; stage of disease etc. to study the effective connectivity, a non-linear technique with more connected regions can be used.
[8]	2012	Zou et al.	Hippocampal-septal computational model	The influence of beta-amyloid on hippocampal network dynamics is identified by estimating the changes in theta band power of hippocampo-septal.	The simulation and analysis are done on homogeneous network connectivity. If there is heterogeneity in the network connectivity it might create some difficulties in the analysis.
[9]	2013	Spies et al.	Probabilistic model for prediction of levels of CSF P-Tau and CSF AB42.	An overall accuracy of 91% has been obtained from this model.	With large dataset of large number of patients, it become difficult to map the stage of disease on one scale as stage of disease may vary from individual to individual. Therefore, some misclassifications were occurred.
[10]	2014	Maia et al.	Theoretical computational model	The effects of concussion and TBI on axonal functionality.	The model was applied to examine the axonal swelling of a single neuron only. In this study, the combined effect of multiple FAS was not clear.
[11]	2014	Abuhassan et al.	Compensation mechanism for synaptic loss in AD	The results show that therapeutics, if they are targeting compensation mechanism then if will be efficient for the treatment of Alzheimer's disease.	For the exploration of synaptic loss and compensation mechanism, modeling of thalamocortical network will enhance the information obtained from this model.
[12]	2018	Grill et al.	"Non-elevated" amyloid PET scan.	90% people decided not to change their routine after knowing that they do not have plaque.	Patients are taken from single site. It will be an important are of future work if patients are taken into different sites of

					disclosure process.
[13]	2018	Dou et al.	Network meta analysis of drugs given to AD patients.	Medication can be given to patients with mild to moderate and moderate to severe AD.	The large sized population creates the heterogeneity in the network and results in cognition among the inhabitants with moderate to severe Alzheimer's disease.
[14]	2019	Baldeiras et al.	Erlangen score tool to estimate the succession of AD from MCI to Dementia.	Patients with higher ES outcome are categorized in AD group and those with lower ES outcome are put in MCI-AD group.	The borderline for each patient may vary considerably. So for that reason, it becomes difficult to examine the ES score with medium values, as to where to put these patients (as in mild to moderate stage or moderate to severe stage).
[15]	2008	Youm et al.	AD vaccine from transgenic tomatoes.	This vaccination was developed so as to prevent or delay the accumulation of β-amyloid.	To give any vaccination to anyone, first of all the immune system of that patient is of first concern. Therefore, the vaccination and its concentration have to be varied for every patient.

2. CONCLUSION

Alzheimer's disease is emerging as major problem globally as there is no cure for Alzheimer's disease and its early detection has not yet discovered. From the above presented literature review we can conclude that although the detection of Alzheimer's disease is still a big question mark, yet a great deal of work for the diagnosis and treatment of it has already been done. However, there can be some more attributes yet to be identified with which the detection of Alzheimer's disease can be done at its mild stage and prevention of it may also be possible.Few gaps are observed in the above study. In some studies, it was not clear how effectively the findings generalize to the study of Alzheimer's disease. Lastly, some more advancement like machine learning techniques can be applied which may help for better generalization of the disease.

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