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Employing Neuronal Networks to investigate the Pathophysiological Basis of Abnormal Cortical Oscillations in Alzheimer's Disease

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Abstract—This paper describes an investigation into the pathophysiological causes of abnormal cortical oscillations in Alzheimer's disease (AD) using two heterogeneous neuronal network models. The effect of excitatory circuit disruption on the beta band power (13–30 Hz) using a conductance-based network model of 200 neurons is assessed. Then, the neural correlates of abnormal cortical oscillations in different frequency bands based on a larger network model of 1000 neurons consisting of different types of cortical neurons is also analyzed. The results show that, despite the heterogeneity of the network models, the beta band power is significantly affected by excitatory neural and synaptic loss. Secondly, the results of modeling a functional impairment in the excitatory circuit shows that beta band power exhibits the most decrease compared with other bands. Previous biological experiments on different types of cultural excitatory neurons show that cortical neuronal death is mediated by dysfunctional ionic behavior that might specifically contribute to the pathogenesis of β-amyloid peptide (Aβ)-induced neuronal death in AD. Our study also shows that beta band power was the first affected component when the modeled excitatory circuit begins to lose neurons and synapses. Alpha (8–12 Hz), gamma (30–50 Hz) and Full frequency (1–70 Hz) band power are affected in a later stage when more severe synaptic loss occurs.

I. Introduction

For the last few decades, Electroencephalography (EEG) has been utilized for diagnosing dementias. EEG is a measure of the electrical activity along the scalp produced by a sufficiently large population of neurons. There is a strong correlation between cognitive deficit and the degree of the EEG abnormality. EEG spectral analysis in AD patients has shown a decrease in the mean frequency, alpha (8–12 Hz) and beta (13–30 Hz) band powers with a parallel increase in delta (1–3 Hz) and theta (4–7 Hz) band powers compared with those of normal elderly subjects [1].

The EEG abnormalities in AD indicate functional and anatomical impairment of the cerebral cortex affected by the disease. More investigations are needed to provide insights to the underlying neurological basis of those abnormalities as well as to couple those findings with the severity of AD. The neuropathology of AD is characterized by an enormous neuronal and synaptic loss in the cerebral cortex and certain subcortical regions, and the formation of both neurofibrillary tangles (NFT) and neurotic plaques (NP). NFT are pathological tangles of hyperphosphorylated tau protein accumulated in the brains of AD patients; it was thought that the number of NFT is directly correlated with neuronal dysfunction as well as indicates the degree of dementia. β-Amyloid peptide (Aβ) is the main component of NP observed in the brains of patients with AD and has been suggested to contribute to the pathogenesis of neuronal degeneration [2].

Understanding the exact role of several Aβ peptide fragments in different types of neurons based on computational modeling may provide a novel approach to reduce neuronal degeneration in patients with AD. A number of studies reported an alteration of neuronal K+ channel function after exposure to Aβ peptide fragments which led to remarkable perturbations in neuronal behavior. These channels provide negative feedback to the membrane potential of neurons. Thus, it regulates the neuronal dynamics including the timing of interspike intervals (time between spikes), setting the resting potential, and keeping action potentials short [3]. Deregulation of K+ channels has been investigated by a number of studies [4].

The goal of this study is to investigate the neural correlates of abnormal EEG dynamics in AD based on computational modeling approaches. Specifically, we examine the effects of neuronal/synaptic loss and deregulation of negative feedback to the membrane potential of cortical neurons (which mainly results from Aβ-induced dysfunctional K+ channels) on the oscillatory activity of cortical networks.

Firstly, the effect of excitatory circuit disruption on beta band power (13–30 Hz) is investigated using a local network model. Then, the investigation is extended to explore the underlying neurological sources of abnormal dynamics in different frequency bands based on a larger network model consisting of different types of cortical neurons.

The paper is outlined as follows. The network models are described in section II. Then, the results and analysis are provided in section III. Finally, discussions and conclusion are presented in sections IV and V, respectively.

II. Network Models

A. Local neuronal network

We simulated a conductance based neuronal network of 200 cells containing 160 excitatory (e–cells) and 40 inhibitory (i–cells) neurons in the baseline (normal) case.

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The cells are connected all–to–all assuming (e–e) synapses are weak within local networks [5]. Parameters and functional forms of the equations are adopted from [6]. Neurons were modeled by Hodgkin–Huxley dynamics, i-cells were of the form,

$$C\left(\frac{dV_i}{dt}\right) = -g_L(V_i - V_L) - g_K n^4(V_i - V_K) - g_{Na} m^3 h(V_i - V_{Na}) - I_{syn,i} + I_0 \quad (1)$$

And the e–cells were modeled by the equations,

$$C\left(\frac{dV_e}{dt}\right) = -g_L(V_e - V_L) - g_K n^4(V_e - V_K) - g_{Na} m^3 h(V_e - V_{Na}) - g_{AHP} w(V_e - V_K) - I_{syn,e} + I_0 \quad (2)$$

Both types of cells have a leak (L), transient sodium (Na) and delayed rectifier potassium (K) current. The e–cells have an additional after–depolarizing potential (AHP) resulting in a slow outward potassium current.

The maximal conductances were g_{Na} = 100 mS/cm^2, g_K = 80 mS/cm^2, g_L = 0.1 mS/cm^2, and g_{AHP} = 0.3 mS/cm^2. Reversal potentials were V_L = - 67 mV, V_K = - 100 mV, and V_{Na} = 50 mV. The capacitances for e- and i-cells were 1 AF/cm^2. The gating variables m, h, n satisfy equations of the form

$$\frac{dx}{dt} = a_x(V)(1 - x) - b_x(V)(x) \quad (3)$$

For x = m, h, n where

$$a_m(V) = 0.32(54 + V)/(1 - \exp\left[\frac{-(V+54)}{4}\right]) \quad (4)$$

$$b_m(V) = 0.28(V + 27)/(\exp\left[\frac{(V+27)}{5}\right] - 1) \quad (5)$$

$$a_h(V) = 0.128 \exp\left[-(V + 50)/18\right] \quad (6)$$

$$b_h(V) = 4/(1 + \exp\left[\frac{-(V+27)}{5}\right]) \quad (7)$$

$$a_n(V) = 0.032(V + 52)/(1 - \exp\left[\frac{-(V+52)}{5}\right]) \quad (8)$$

$$b_n(V) = 0.5 \exp\left[-(57 + V)/40\right) \quad (9)$$

The gating variable w is represented by

$$\frac{dw}{dt} = (w_\infty(V) - w)/\tau_w(V) \quad (10)$$

$$w_\infty(V) = 1/(1 + \exp\left[\frac{-(V+35)}{10}\right]) \quad (11)$$

$$\tau_w(V) = 400/(3.3 \exp\left[\frac{(V+35)}{20}\right] + \exp\left[\frac{-(V+35)}{20}\right]) \quad (12)$$

Synaptic currents were modeled as

$$I_{syn,\alpha} = g_{i\alpha} s_{i,tot}(V_\alpha - V_{in}) + g_{e\alpha} s_{e,tot}(V_\alpha - V_{ex}) \quad (13)$$

For α = e, i. Reversal potentials for AMPA and $GABA_A$ were V_{ex} = 0 mV and V_{in} = - 80 mV, respectively. The synaptic gates satisfy:

$$s_{\alpha,tot} = \frac{1}{N_\alpha} \sum_{\alpha-cells} s_\alpha \quad (14)$$

$$\frac{ds_\alpha}{dt} = a_\alpha\left(1 + \tanh\left(\frac{V_\alpha}{4}\right)\right)(1 - s_\alpha) - (s_\alpha/\tau_\alpha) \quad (15)$$

where a_e = 20/ms, a_i= 1/ms, τ_e = 2.4 ms, and τ_i= 12 ms. The inhibitory $GABA_A$ conductances, g_{ie} and g_{ii} are 5 mS/cm^2 and 10 mS/cm^2, respectively. The excitatory conductances were g_{ee} = 0.01 mS/cm^2 and g_{ei} = 0.05 mS/cm^2.

The model time was 2000 ms and spike trains were assessed after 1000 ms allowing a settlement period of 1000 ms. Gaussian noise generated by a wiener process was added to the voltages at each integration step. The magnitude of the noise was 0.5 for the e-cells. The equations were integrated using Euler's method with a time step of 0.025 ms.

To achieve heterogeneity, the input currents (I_0) were varied in the range from 0.6 to 2.0 μA/cm^2 to the e-cells and from 1 to 1.1 μA/cm^2 to the i-cells. The release of neuromodulators such as ACh in the rest state is lower than that in the active states. Low ACh increases the AHP-currents (I_{AHP}). This motivates the choice of relatively strong AHP-currents (I_{AHP}) [6].

1) Hypothesis testing

Based on the local network model, we have investigated the effect of excitatory circuit disruption on the beta band power (13–30 Hz). To achieve our aim, we have first run the model with physiological (normal) values of all parameters for 25 trials. Then, we have repeated the same procedure but with the following values of the number of excitatory neurons (Ne): 150, 140, 139, 135 and 130 e-cells.

The Fast Fourier transform (FFT) has been applied on the spiking train produced by each network setup to calculate the power spectra within beta band. One–way repeated measures ANOVA has been used to analyze significance of the difference in beta band power between the physiological (baseline) case and cases with abnormal ratio of e-cells to i-cells (corresponding to AD groups). *P* values less than 0.05 indicate a significant difference.

B. A larger network model

Spiking dynamics of neurons were simulated based on Izhikevich's model of spiking neurons [7], which can reproduce the firing patterns of all known types of hippocampal, cortical, and thalamic neurons. The spiking neuron can be expressed in the form of ordinary differential equations (16), (17) and (18).

$$\frac{dV}{dt} = 0.04 * V^2 + 5 * V + 140 - u + I \quad (16)$$

$$\frac{du}{dt} = a(bV - u) \quad (17)$$

with the auxiliary after-spike resetting

$$\text{If } V \geq 30 \text{ mV then } V \leftarrow c,\ u \leftarrow u + d \quad (18)$$

where the dimensionless variables V and u represent the membrane potential and the recovery variable of the neuron respectively. The recovery variable u provides negative feedback to V, and it corresponds to the inactivation of Na+ ionic currents and activation of K+ ionic currents [7]. Dimensionless parameters a, b, c and d can be tuned to simulate the dynamics of inhibitory and excitatory neurons. Parameter b describes the sensitivity of the recovery variable u to the subthreshold fluctuations of the membrane potential V. Greater values of b couple V and u more strongly resulting in possible subthreshold oscillations and low-threshold spiking dynamics [7].

Spiking networks of 1000 neurons of different types, fully and randomly connected to each other with no plasticity were simulated to investigate a number of hypotheses about the underlying causes of abnormal cortical oscillations in AD patients. The networks were stimulated by a random

thalamic current at each time step. We have used MATLAB® software to simulate the networks in real time (resolution 1 ms). Setting the parameters of the model to physiological (normal) settings represents the physiological case. The ratio of excitatory to inhibitory neurons is 4 to 1 inspired by the anatomy of the mammalian cortex [7]. Model time was 30,000 ms, spike trains were computed after 29,000 ms allowing a settlement period of 29,000 ms.

1) Hypothesis testing

The number of e-cells has been varied from 794 to 764 e-cells to simulate the effect of excitatory circuit disruption on the power spectra of different frequency bands; the length of each step is 2. In addition, we have simulated how the enhancement of negative feedback to the membrane potential in e-cells can shift the dynamics of the network by decreasing parameter b (17). The power spectra for delta (1–3 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta1 (13–18 Hz), beta2 (19–21 Hz), beta3 (22–30 Hz), gamma (30–50 Hz), and full (1–70 Hz) frequency bands were assessed. The categorization for the frequency bands is based on [8].

III. RESULTS

A. Decrease in beta band power induced by loss of excitatory neurons and synapses in the local network model.

A significant decrease in beta band power was observed after the excitatory circuit losses more than 20 e–cells (number of e–cells becomes <= 139, loss rate >= 13 %, $P < 0.05$) as illustrated in Fig. 1.

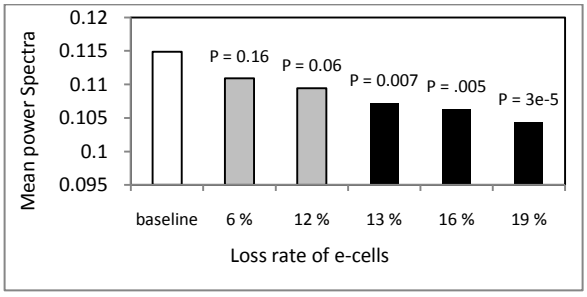

Fig. 1. Mean beta band power (13–30 Hz) for a physiological case (baseline) and cases with reduced e–cells. Black bars correspond to significant differences. The number of trials is 25 for each setup.

We refer to this point as a break down point since the power spectra of beta rhythm exhibits a significant decrease after this point. In the network model, the death of each e-cell is associated with a synaptic loss of 319 excitatory synapses since the network is fully connected.

B. Effects of varying the number of excitatory neurons on the oscillatory activity of the larger network model.

The power spectrum averages of alpha, beta3, gamma and Full frequency bands are significantly decreased when decreasing the number of e-cells from 794 to 764 (decreasing excitation). It is expected that reducing Ne increases the inhibition in the network and slows down the spiking activity. From Table I, we can see that the power spectrum is shifted to lower frequencies with a parallel decrease in the coherence of fast rhythms. The analyses shows that the significant decrease started in the full and beta3 bands (Ne=782). Then, gamma and alpha bands were affected in later stages (Ne=770, 766 and 764). The power spectrum in delta, theta, beta1 and beta2 bands was not significantly decreased.

TABLE I
MEAN POWER SPECTRA AFTER NEURAL/SYNAPTIC LOSS

Frequency band	Min. value [a]	Max. value	Control value [b]	Decrease percentage
Delta	3.498	3.784	3.737	6.4%
Theta	2.71	3.11	3.104	12.7%
Alpha	3.178	4.322	4.236	25%
Beta3	6.125	7.326	7.326	16.4%
Gamma	13.15	15.285	15.034	12.5%
Full	44.25	50.6	50.306	12%

[a] The minimum mean value across network setups. Number of setups is 16 ((794-764)/2). 10 trials for each network setup.
[b] The mean power spectra after simulating the model with physiological values of all model's parameters. (Number of trials equals 10).

C. Effects of varying parameter b for e-cells on the oscillatory activity of the larger network model.

As presented in Table II, there are higher shifts from alpha, beta and gamma bands than slower frequency bands. The beta2 band power is the most affected one. Again, decreasing parameter b (17) for e-cells up-regulates the negative feedback u to the membrane potential V (16), which results in high-threshold spiking dynamics and decreases the spiking activity of e-cells. "This accounts for the activation of K^+ ionic currents and inactivation of Na^+ ionic currents [5]". The power spectrum in theta band was not significantly decreased.

TABLE II
MEAN POWER SPECTRA AFTER VARYING PARAMETER B FOR E-CELLS

Frequency band	Min. value	Max. value	Control value	Decrease percentage
Delta	3.208	3.797	3.737	14.2%
Theta	2.544	3.230	3.104	18%
Alpha	2.937	4.236	4.236	30.7%
Beta1	2.671	3.941	3.579	25.4%
Beta2	1.105	1.863	1.787	38.7%
Beta3	5.359	7.339	7.326	26.9%
Gamma	11.557	15.298	15.034	23.1%
Full	39.326	50.306	50.306	21.8%

Parameter b (17) for e-cells was decreased from 0.1995 to 0.195. Control value is 0.2. Length of each step is 0.0005. (10 trials)

IV. DISCUSSION

A. Structural changes

It is commonly thought that an increase in theta band activity appears in the early stages of AD with a parallel

decrease in beta activity, which is followed by a decrease in alpha band activity at a later stage [1]. Delta activity increases later during the course of the disease.

In the current study, beta rhythm has been investigated (along with other rhythms using the larger network model) with two network models. Despite the heterogeneity of the network models, we find that the power spectrum of beta rhythm is significantly decreased by excitatory neural and synaptic loss but not inhibitory neural and synaptic loss. We also find that the significant decrease begins in the beta3 band (upper beta) when Ne was 782. Then, gamma and alpha bands were affected in later stages (Ne=770, 766 and 764). The sequence of gradual changes in faster bands is compatible with EEG studies [1]. Although the mean power spectrum of the full band is significantly decreased, slower bands (delta and theta) are only slightly affected by the decrease and most of signal power was shifted from fast bands toward slow bands.

Reference [9] emphasized that the decreased activity in alpha, beta and gamma waves are related to changes in excitatory circuit activity. This study involved the analysis of a large EEG dataset using Global Field Synchronization (GFS), a novel measure to quantify global EEG synchronization. A high GFS index for a certain frequency band reflects increased functional connectivity between brain processes. The patient's results showed increased GFS values in the delta band, and decreased GFS values in alpha, beta, and gamma frequency bands, supporting the disconnection syndrome hypothesis [9] and "to be published" [10]. Other AD studies reported decreased synchronization of alpha band [11]. It was suggested that deterioration in excitatory synaptic pathway during AD biased the dynamics towards increased inhibitory activity and affected alpha rhythmic activity [11].

B. Functional changes.

It was demonstrated that cortical excitatory neuronal death is mediated by the enhancement of outward K+ current and such enhancement might specifically contribute to the pathogenesis of (Aβ)-induced excitatory neuronal death [4]. The results in [4] showed that Aβ exposure induce an up-regulation in the delayed rectifier K+ current I_K, an increase in maximal conductance and a shift in its activation voltage relationship toward hyperpolarized levels [4].

The up-regulation of this type of K+ currents provides a more negative feedback to the membrane potential of e-cells followed by neuronal death. We speculate that the neural mechanism that underlies the sequence of abnormal changes into EEG of AD can be described by inspecting the results in Table II which showed a higher shift from upper frequency band powers, in particular, the power spectrum of beta2 rhythm. The significant decrease within beta band power appears also (before other rhythms) when decreasing Ne, followed by a break down in other frequency bands when Ne decreases more and more (increased rate of neuronal and synaptic death). To our knowledge, this is the first study that investigates the neural correlates of abnormal cortical EEG dynamics in AD using computational neuronal models. However, A recent modeling study of the hippocampal CA1 and medial septal regions has proposed that hippocampal theta band power is increased as a result of Aβ-induced reduction in A-type potassium current I_A in e-cells, "to be published" [12]. This suggests the differential vulnerability of neurons and synapses in different cortical and sub-cortical areas to Aβ fragments.

V. CONCLUSION

The impairment of excitatory circuitry appears to play an important role in abnormal oscillatory activity of the neuronal networks and this is supported by our study which uses a simple network models. Furthermore, the observation that the death of e-cells is preceded by dysfunctional behavior and changes in the ionic channels has been investigated in the study. The dynamical changes of the rhythmicity in the network as a result of alterations in the negative feedback for membrane potential in e-cells have been focused on. Future investigations will be based on a network consisted of 100,000 cortical neurons, distribution of axonal conduction delays, long-term spike-timing-dependent synaptic plasticity (STDP), receptor kinetics, and short-term plasticity. The network structure is informed by the organization of the cerebral cortex.

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