INVESTIGATION OF THE RELATION BETWEEN DOPAMINE DEPLETION AND THE SLOWING OF ALPHA RHYTHM IN ELECTROENCEPHALOGRAM OF THALAMUS

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***Abstract*—** A hybrid computational model of thalamo-cortical circuitry and basal ganglia is used to investigate the relation between the electroencephalogram (EEG) changes within the alpha frequency bands in thalamic region depending on the decrease in the dopamine level in striatum. Since it is known that in the diseases such as Alzheimer and Parkinson, the level of dopamine decreases, the related changes in thalamic region is investigated considering the dopamine depletion. The diseases affects the dopamine decrease in different ways, such that in Parkinsonian disease (PD), the total amount of dopamine affecting striatal neurons decreases whereas in Alzheimer disease (AD), the dopamine level decreases mostly in D2 dopamine receptor neurons. Therefore, these differences are analyzed to investigate the slowing of alpha rhythm on EEG of thalamus by using the modified mass model of thalamic region. It is observed that the decrease in the amount of dopamine causes shift of the power in alpha bands to lower frequencies. When the dopamine level is decreased in D1 and D2 type MSN neurons, the slowing of alpha rhythm in EEG of thalamus is prominent.

***Keywords*—** *Alzheimer disease, EEG, dopamine, Parkinson disease*

1. INTRODUCTION

PARKINSON'S (PD) and Alzheimer's disease (AD) are the two of the most common seen progressive neurodegenerative disorders. PD is characterized by four primary motor symptoms: akinesia, bradykinesia, muscle rigidity and resting tremor. The brains of Parkinson's disease dementia (PDD) patients show extensive cholinergic loss as well as dopamine (DA) depletion [1]. In PD, the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc) of the midbrain leads to the emergence of pathological activities in the basal ganglia–thalamic neural loop [2]. On the other hand, the AD is characterized by cognitive dysfunction and impairments in memory, the difficulties with memory, language, problem solving, since the neurons in the parts of the brain involving in cognitive function are damaged or destroyed. Neuropathologically, AD is characterized by the presence of extracellular amyloid β as plaques, hyper-phosphorylated microtubule associated protein tau and neurotic plaques that are composed of both amyloid β and tau. [3,4]. VTA and substantia nigra (SN) are the brain areas that are the origin of the dopaminergic cell bodies of the brain dopamine system. From the investigations in a murine model of AD, a significant loss of dopaminergic neurons in Ventral tegmental area (VTA), accompanied by reduced hippocampal innervation and declining memory was observed [5].

The alpha rhythm (8–13 Hz) in EEG signal is related to AD and PD. A transition of EEG from the alpha to the theta (4–7 Hz) band in an awake state is associated with the several neurological disorders including PA, and is termed as thalamocortical dysrhythmia (TCD). A similar symptom in AD is termed as "slowing" (a decrease of dominant frequency) of the alpha rhythms [6]. When compared to the resting state EEG rhythms of healthy elderly subjects, AD patients showed an amplitude increase of widespread delta and theta sources and an amplitude decrease of posterior alpha (8–13 Hz) and/or beta (13–30 Hz) sources. Diminishing power within the alpha band, referred to in literature as 'slowing' of alpha rhythms, is identified as a definite biomarker in the EEG of AD patients [7-10].

In this work, the influences of dopamine decrease in alpha band of EEG in thalamic region is investigated, since the diseases such as Parkinson and Alzheimer are related to the dopamine depletion in the striatum region of basal ganglia. Also, since a reduced number of D2 receptors in the striatum have been observed in AD [11], together with total reduction, the reduction only in D2 dopamine level is also investigated. The mass model of thalamus region and Izhikevich neuron based network model of basal ganglia are used in the analyses. It is observed that decrease in dopamine causes the shift of power to lower frequency component in alpha band, phenomena named as slowing in alpha rhythm. The total decrease (D1 and D2) in dopamine has prominent effect on slowing of alpha rhythm compared to only D2 dopamine level decrease.

2. BASAL GANGLIA THALAMIC NETWORK

The network consists of the basal ganglia and the thalamic regions of the brain as shown in Fig.1. The basal ganglia is interconnected with the cerebral cortex, thalamus, and other brain areas. It is associated with the functions, such as control of voluntary motor movements, procedural learning, habit learning, cognition and emotion. The main structures comprising the basal ganglia are the striatum, globus pallidus, substantia nigra and subthalamic nucleus (STN). The globus pallidus is divided into two functionally distinct parts, called the internal and the external segments, abbreviated as GPi and GPe. Substantia nigra has two parts: the pars compacta (SNc) and the pars reticulata (SNr). The striatum, the largest structure of the basal ganglia, mainly consists of Fast Spiking Interneurons (FSI) and Medium Spiny Neurons (MSN) including D1 and D2 type dopamine receptors.

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Manuscript received May 20, 2019; accepted Jun 10, 2019.

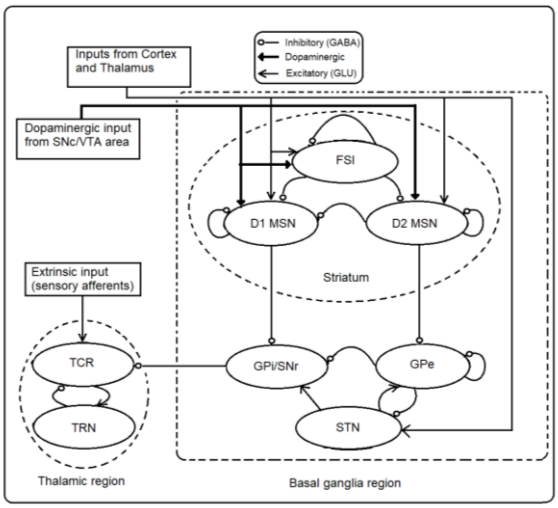

Fig. 1. Structure of basal ganglia thalamocortical network

In primates the SNr and GPi are part of separate circuits, with different target areas and sources of activity, but, despite these differences, GPi and SNr are often considered as a single structure due to their closely related inputs and outputs, also SNr works in unison with GPi, and the SNr-GPi complex inhibits the thalamus, therefore the the SNr-GPi are considered as a single neuronal population in the present model.

The striatum, GPi and GPe contain primarily GABAergic neurons having inhibitory effects on their connected post synaptic neurons. D1 MSN neurons project primarily to the output nuclei GPi and SNr, whereas D2 neurons project to the GPe. The GPe receives input also from STN neurons and other GPe neurons over local axon collaterals which have an inhibitory influence. The GPe sends an inhibitory projection to GPi and to STN. The subthalamic nucleus produces the neurotransmitter glutamate, which excites both the GPe and GPi/ SNr output nuclei. Striatal activity has excitatory effect on the thalamus via the D1 MSN neurons connection from the striatum to the output nuclei called direct pathway, and an inhibitory effect via the D2 MSN neurons connection to the output nuclei over GPe and the STN called indirect pathway. The two external inputs to network are glutamatergic cortical input and dopamine neurotransmitter originating from SNc region [2,12].

In the context of analyzing the changes in Alpha Rhythm in the case of diseases such as AD and PD, the thalamic region model is based on the previous work by Bhattacharya *et al*. [13]. In the present model, thalamic region consists of thalamo cortical relay (TCR) cells and thalamic reticular nucleus (TRN) considered as a mass model. The brain alpha rhythms are the most prominent in EEG from the occipital lobe in resting state. The external input to thalamic region represents the background firing rate represented as spikes per second of the retino-geniculate neuronal populations and is simulated by a Gaussian white noise. The inhibition effect of GPi/SNr part is obtained via connection over TCR population through the synaptic contact called as C_4. The detailed network model is given in Fig. 2.

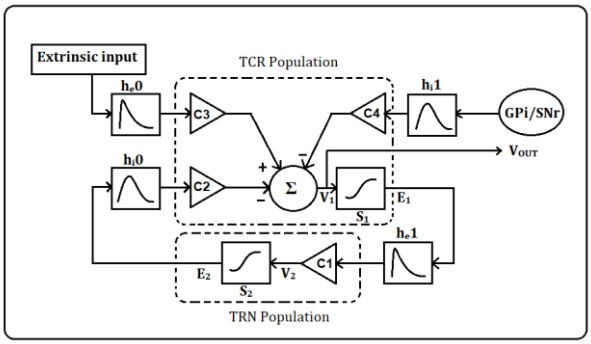

Fig. 2. Thalamic region mass model

2.1. Modeling of Basal Ganglia Network

The basal ganglia and thalamic network structure used in this work is initially proposed in the work by Cakir [14]. The basal ganglia part of network is modeled with Izhikevich neurons and consists of Striatum, GPi/SNr, GPe and STN neuronal population, each comprised by 20 neurons. Beside striatum, the other populations are modeled by the simplified form of Izikhevich neuron model given as,

$$\begin{aligned} \dot{v} &= 0.04v^2 + 5v + 140 - u + I \\ \dot{u} &= a(bv - u) \\ if\ v \geq 30\,mV, then\ v \rightarrow c, u \rightarrow u + c \end{aligned} \quad (1)$$

where C is the membrane capacitance, v and u represent the membrane potential of the neuron and the membrane recovery, respectively. a, b, c, and d are dimensionless parameters. The input current I_i of any i'th neuron in this populations is expressed as $I_i = I_i^{app} + I_i^{syn}$.

The striatum consist of 3 types of neurons, roughly 10 % of them are FSI neurons, the half of the rest consists of D1 receptor type MSN and the other half of D2 receptor type MSN's. FSI neurons in the striatum have inhibitory GABAergic connections with the other FSI neurons and D1 and D2 MSN neuronal population. The D2 MSN neurons has inhibitory GABAergic connection with other D2 MSN neurons, D1 MSN neurons population and GPe neurons. The D1 MSN neurons has inhibitory effect on the other D1 MSN neurons and GPi and SNr populations. Since the effect of change in the amount of dopamine in striatum is investigated, the role of dopamine is included in neuron model. Dopamine has a dual action on MSNs; it inhibits the (D2-type) MSNs in the indirect pathway and excites (D1-type) MSNs in the direct pathway. The neuron models of D1 and D2 type MSN neurons and FSI neurons including the effect of dopamine are as,

$$\begin{aligned} C\dot{v}_{D1} &= k(v_{D1} - v_r)(v_{D1} - v_t) - u + I + \phi_1 g_{DA}(v_{D1} - E_{DA}) \\ C\dot{v}_{D2} &= k(1 - \alpha\phi_2)(v_{D2} - v_r)(v_{D2} - v_t) - u + I \\ C\dot{v}_{fs} &= k[v_{fs} - v_r(1 - \eta\phi_1)](v_{fs} - v_t) - u_{fs} - I \end{aligned} \quad (2)$$

where $\phi_1 g_{DA}(v_{D1} - E_{DA})$ is for simulating the hyperpolarizing effect of D1 activation. ϕ_1 is the parameter for specifying the level of dopamine for D1, $k(1 - \alpha\phi_2)$ is included to model increased sensitivity to the injected current following D2 activation, where ϕ_2 is the amount of dopamine [15]. Here I denotes the currents consisting of the externally applied and the synaptic current, $(I = I^{out} + I^{syn})$. The externally applied current is modeled as,

$$I^{out} = I_o + \sigma I_{cortical} \quad (3)$$

where I_o and σ are the constants, $I_{cortical}$ is a pulse shaped signal with unit amplitude and frequency of 2 spike/s, simulating cortical input [15]. The synaptic current of any i'th MSN neuron is given in Eq. 4.

$$I_i(t) = g_{gaba\_j} \sum_j r_{ij}(t - \tau_{ij}) \left[E_{gaba\_j} - V_i\right] \quad (4)$$

where g_{gaba_j} is the chemical conductivity strengths, and τ_{ij} represents time delays from *j*'th presynaptic neurons to *i*'th postsynaptic neuron but time delay in this work was assumed zero during analysis. E_{gaba_j} is the reversal potentials for the inhibitory synapses and was taken as E_{gaba_j} =- *60 mV*. For each spiked connected neuron, the connection strength between these neurons is updated as $r_{ij} \leftarrow r_{ij} + \omega_{ij}$, here ω_{ij} is the inhibitory synaptic strength from neuron j to neuron i [16, 17,18]. During simulations the synaptic strength was taken as ω_{ij}=0.2 for all striatal neurons. r_{ij} is the dynamic variable that decreases exponentially depending on decay time τ_s as given in Eq. 5.

$$\tau_s \dot{r}_{ij} = -r_{ij} \quad (5)$$

Apart from MSN, the FSI neurons have synaptic connection only with other FSI's and also there exist a gap junction between FSI neurons that provide an extra current of electrical type. Therefore synaptic input for any I'th FSIs is,

$$I_i = g_{gaba_j} \sum_j r_{ij}\left(t - \tau_{ij}\right) \left[E_{gaba_j} - V_i\right] \ (1 - \varepsilon\phi_2) + g_{gap} \sum_k [V_k - V_i] + I^{out} \quad (6)$$

where g_{gap} is the constant electrical synaptic strength from neuron *k* to *i*. V_k and V_i are pre and postsynaptic neuron's membrane potential. The network parameters are determined by considering the works by [2,12,18]. The parameters can be found in [14].

For investigating only the influences of dopamine decrease in the striatum sub network, the predefined connection between basal ganglia sub networks is established and kept the same during analyses. Every sub networks of basal ganglia is represented by the populations of 20 Izhikevich neurons having connectivity with the other populations as described in Fig 1.

Based on the findings mentioned in [2, 12], the connectivity for the rest of the basal ganglia network is established randomly but such that every GPe neuron receives inhibitory input from 2 MSN D2 neurons and two GPe neuron, and the excitatory input from 3 STN neuron. Every neuron from GPi/SNr population receives inhibitory input from two MSN D1 neurons, one GPe neurons and excitatory input from one STN neurons. Every neuron from STN neuronal population receives inhibitory input from two GPe neurons. STN neurons receive the applied currents from the cortical region also. The inhibitory connection to the thalamic region is from GPi/SNr population. However, since the mass model is used for the thalamic region, the inhibitory signal is obtained by using mean firing value of all neurons in this population.

2.2. Mass Modeling of Thalamic Network

The mass model of thalamic region was constructed by TRN and TCR cell populations. Every neuronal population in the model given in Fig. 2 is considered as a single entity having a soma which generates membrane potential *v(t).* It is the sum of potential changes due to extrinsic and intrinsic inputs subsequently transformed into a mean firing rate using a sigmoid function. The TCR cell population receives excitatory input from an extrinsic source and inhibitory signal from GPi/SNr population. Since Alpha Rhythms are dominant in cortical EEG while a subject is in a relaxed but awake state, the extrinsic source represents a background firing activity of the neurons in the sensory pathway. They are simulated as Gaussian white noise having a mean, μ and standard deviation, ϕ.

The second-order differential equation corresponding to the postsynaptic membrane potentials of TCR and TNR neuronal masses are given as first order differential equations in the form of

$$\begin{aligned}
\dot{x}_{ret1} &= x_{ret2} \\
\dot{x}_{ret2} &= \frac{H_e}{\tau_e} P(t) - \frac{2}{\tau_e} x_{ret2} - \frac{1}{\tau_e^2} x_{ret1} \\
\dot{x}_{tcr1} &= x_{tcr2} \\
\dot{x}_{tcr2} &= \frac{H_e}{\tau_e} S\left(C_3 x_{ret1} - C_2 x_{trn1} - C_4 x_{GPi_SNr1}\right) - \frac{2}{\tau_e} x_{tcr2} - \frac{1}{\tau_e^2} x_{tcr1} \\
\dot{x}_{GPi_SNr1} &= x_{GPi_SNr2} \\
\dot{x}_{GPi_SNr2} &= \frac{H_i}{\tau_i} \Delta V_{GPi/SNr} - \frac{2}{\tau_i} x_{GPi_SNr2} - \frac{1}{\tau_i^2} x_{GPi_SNr1} \\
\dot{x}_{trn1} &= x_{trn2} \\
\dot{x}_{trn2} &= \frac{H_i}{\tau_i} S(C_1 x_{tcr1}) - \frac{2}{\tau_i} x_{trn2} - \frac{1}{\tau_i^2} x_{trn1}
\end{aligned} \quad (7)$$

The output of the model is the membrane potential of the TCR cell population defined as

$$V_{tcr} = C_3 x_{ret1} - C_2 x_{trn1} - C_4 x_{GPi\_SNr1} \quad (8)$$

The parameter $H_{e,i}$ in the equation tunes the maximum amplitude of PSPs and $\tau_{e,i}$ is the lumped representation of the sum of the rate constants of passive membrane and other spatially distributed delays in the dendritic tree, where *e* represent excitatory and *i* represent inhibitory state [19]. Each connectivity parameter, C_i represents the synaptic contact. The connectivity parameter, C_4 reflects inhibitory effect of GPi/SNr neuronal population activity on TCR neuron mass. The sigmoid functions S(·) in (7) transform the membrane potential of a post-synaptic cell population into firing rate and is defined as $S(v) = \frac{V_{max}}{1+e^{r(V_0 - v)}}$ where V_{max} is maximum firing rate of neuron population, V_0 is value of the potential for which a 50% of firing rate is achieved, also viewed as firing threshold, and *r* is the slope of sigmoid function.

$P(t)$ is extrinsic input simulated as Gaussian white noise. The $\Delta V_{GPi/SNr}$ is the deviation from the GPi/SNr population mean activity value obtained for the parameter set representing a healthy state (dopamine value 100%) dynamics in GPi/SNr population. This deviation is obtained as a difference of GPi/SNr mean activity values depending on the decreased value of dopamine. The parameter values of thalamic network used in simulations are given in Table 1.

TABLE 1. The parameters of mass model of thalamic region

Parameter	Value	Parameter	Value
H_e (mV)	3.25	V_0 (mV)	5
H_i (mV)	22	C_1 (%)	35
τ_e (mV^{-1})	10	C_2 (%)	15
τ_i (mV^{-1})	20	C_3 (%)	7
V_{max} (s^{-1})	5	C_4 (%)	10
r (mV^{-1})	0.56		

3. SIMULATION RESULTS

Since the dopamine level decrease in the PD and AD, the neuronal activity of proposed network is analyzed by reducing the amount of dopamine in D1 and D2 MSN neurons. The influences of decrease of dopamine in striatum and slowing in alpha rhythms in thalamic network depending on these decreases are investigated.

The basal ganglia and thalamic network model's equations are solved in MATLAB environment. The forward Euler method with a time-step of 0.1 ms is used in the simulations. For 8-13 Hz frequency alpha band analysis in thalamic region, a time interval of 60 seconds is used. The Fast Fourier Transform (FFT) is used to obtain the power spectrum of alpha rhythm. Prior to power spectrum analysis of alpha rhythm, the first 3 and last 2 seconds of simulation output vector V_{tcr} are discarded and the remaining part of the signal is sampled at 250 Hz and bandpass filtered, with a lower and upper cut-off frequencies of 7.5 and 13.5 Hz (alpha band), respectively, using a Butterworth filter of order 10.

The striatum region activity affects the remaining basal ganglia network via D1 MSN and D2 MSN neurons. The decrease in dopamine from its normal value, resembling the effect of disease, causes an increased activity in GPi/SNr neural population. Due to the nature of the diseases considered in this work, it is assumed that the network parameter changes occur slowly and progressively. Therefore, assuming that in healthy state, there is no disease based inhibitory effect to thalamic population from GPi/SNr, but, depending on the decrease in dopamine, there is emerging disease based inhibitory signal increase, it is decided to model inhibitory signal from GPi/SNr network to thalamus as deviation from mean value obtained in healthy state. The obtained difference $\Delta V_{GPi/SNr}$ is used as an input from basal ganglia to thalamic region mass model.

The parameter values in striatum are changed in such a way that the D1 and D2 MSN neurons' dopamine level is decreased from %100 to %50 and % 0. During the investigations, the cortical input and randomly produced white Gausian formed thalamic external input are kept the same. The results obtained for the initial parameter values are used as reference.

A short time interval, showing deviation in the membrane potentials of some neurons from basal ganglia network for dopamine value of % 100 are given in Fig. 3 as an example. In the network consisting of 80 neurons, the first 20 neurons represents the striatum region, the second 20 neurons represent GPi/SNr region, the 41-60 neurons are GPe population and the latest 20 neurons comprise STN population. The raster plots of all neurons in this time interval are given in Fig 4.

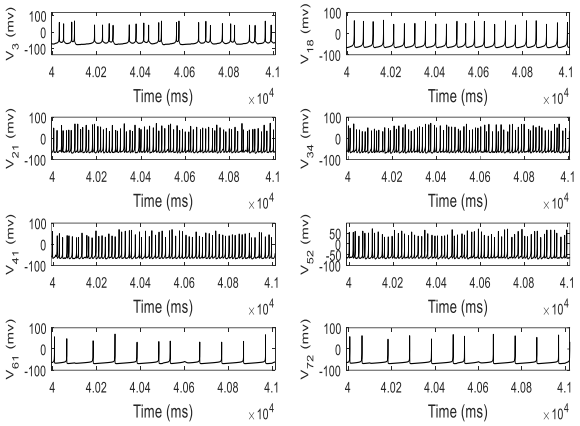

Fig. 3. The deviation of neuron membrane potentials between 40 and 41 s.

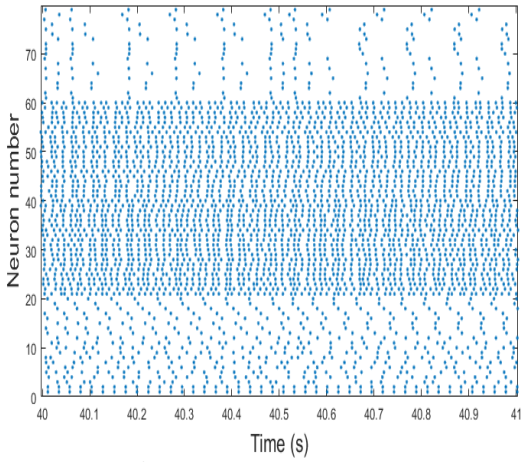

Fig.4. The raster plot of neuron populations in time interval between 40 and 41s.

From GPi/SNr population activities obtained for different dopamine values, the deviation from mean spiking value ($\Delta V_{GPi/SNr}$) is obtained and given in Table 2. As seen from table, the maximum deviation from the mean activity value is observed when D1 and D2 MSN neurons dopamine level decrease together. The decrease only in D2 dopamine level does not lead much increase in GPi/SNr population mean spiking value.

TABLE 2. The reference mean spiking value in GPi/SNr population and the deviation from this reference depending on dopamine decrease.

D1 MSN dopamine value (%)	D2 MSN dopamine value (%)	GPi/SNr population mean spiking value $V_{GPi/SNr,\ mean}$ (spike/s)	Deviation from the reference mean spiking value ($\Delta V_{GPi/SNr}$)
100	100	75.6262 (Reference value)	0
50	50	76.0248	0.3986
0	0	76.8706	1.2444
100	50	75.6779	0.0517
100	0	75.6607	0.0345

The effects of dopamine level on slowing in alpha rhythms are investigated by decreasing the value of dopamine from % 100 to %50 and % 0 respectively. The results obtained for the synaptic contact C_4=10 are given in Fig. 5.

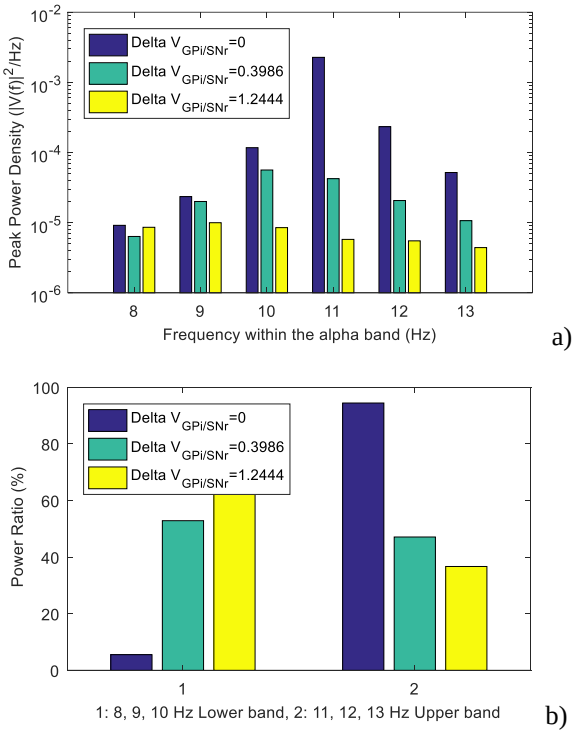

Fig. 5 a) Power density in alpha frequencies obtained for C_4=10 and D1 and D2 dopamine values of 100% , 50% and 0%. b) Power ratio in lower and upper alpha bands for corresponding dopamine values.

From Fig. 5a, it is observed that the ratio of power in lower frequencies (8-10 Hz) of alpha band increases compared to that of higher frequency (11-13 Hz) values. For a better view, the ratios of power related to the deviation in inhibitory signal $\Delta V_{GPi/SNr}$ are given in Fig. 5b. While the power in higher frequency of alpha band is over 90% for normal dopamine values, it decreases below 40% for zero dopamine value, meaning that power shifted to lower alpha frequency band, also named slowing in alpha rhythm is observed.

Since a reduced number of D2 receptors in the striatum has been observed in AD, in addition to the investigation of total reduction of dopamine, only the D2 dopamine level reduction is also investigated. The results obtained for 50% and 100% reduction of D2 dopamine level are given in Fig. 6. For dopamine level of 50% and 0% in D2, the deviations of inhibitory signal $\Delta V_{GPi/SNr}$ from its mean value are obtained as 0.0517 and 0.0345 respectively. Since the deviation from mean value is not as much as that observed when D1 and D2 MSN neurons dopamine level decrease together, the power in higher alpha bands does not change very much for the synaptic contact value of C_4=10. But for higher synaptic contact value such as C_4=100, the shift of power to lower alpha bands is observed as that seen in both D1 and D2 MSN neurons dopamine level decrease (Fig. 7). It is interesting observation that for 0% value of D2 dopamine, the deviation of inhibitory signal $\Delta V_{GPi/SNr}$ from its mean value is higher than that obtained for 50% decrease in dopamine. Therefore, the shift in the power to lower alpha band is not as high as that seen for 50% D2 dopamine decrease.

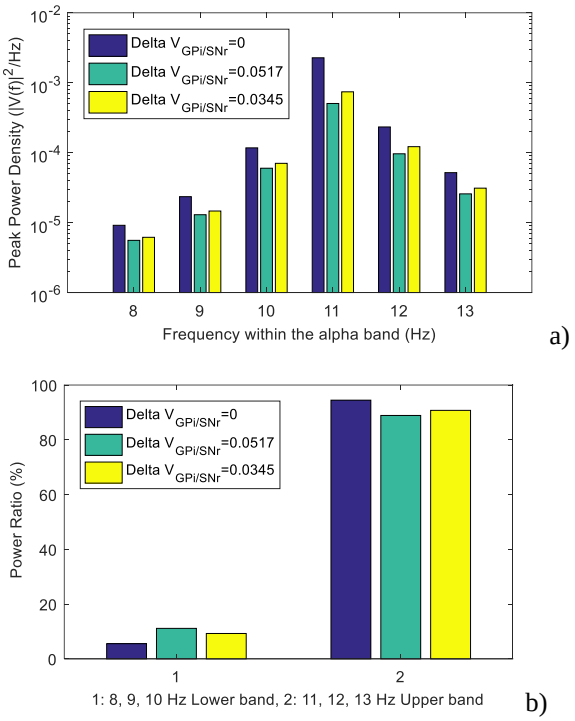

Fig. 6a) Power density in alpha frequencies obtained for C_4=10 and D2 dopamine values of 100% ,50% and 0%. The D1dopamine value is 100%. b) Power ratio in lower and upper alpha bands for corresponding dopamine values.

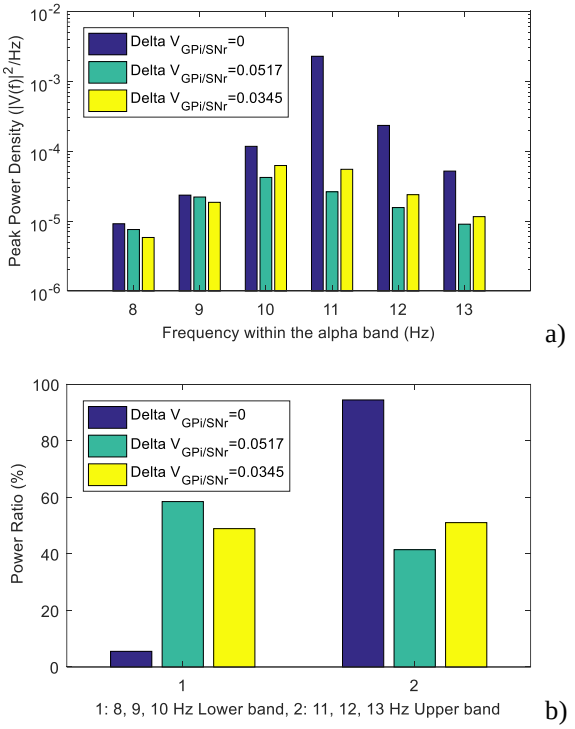

Fig. 7a) Power density in alpha frequencies obtained for C_4=100 and D2 dopamine values of 100% , 50% and 0%. The D1dopamine value is 100%. b) Power ratio in lower and upper alpha bands for corresponding dopamine values.

4. CONCLUSIONS

The relation between EEG changes within the alpha frequency bands in thalamic region due to the decrease in the dopamine level in striatum is investigated. For that purpose, a hybrid computational model of thalamo-cortical circuitry and basal ganglia is used. The mass model of thalamus region and Izhikevich neuron based network model of basal ganglia are used in the analyses. It is observed that the decrease in the amount of dopamine cause shift of the power in alpha bands to lower frequency values. When the dopamine levels of D1 and D2 MSN neurons decrease all together, the higher level of increasing inhibitory signal to thalamus is observed. This leads to a prominent slowing of alpha rhythm in EEG of thalamus. When only the dopamine level in D2 type MSN neurons is decreased, the slowing of alpha rhythm is observed for higher C_4 synaptic contact values. This is also a cognitive status of the brain.

ACKNOWLEDGMENT

This work is supported by TUBITAK BIDEB (2219).

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