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Authors(s)	Farokhniaee, AmirAli, Lowery, Madeleine M.
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A Thalamo-Cortex Microcircuit Model of Beta Oscillations in the Parkinsonian Motor Cortex

Author List: AmirAli Farokhniaee and Madeleine M Lowery

Corresponding Author: Dr AmirAli Farokhniaee
School of Electrical and Electronic Engineering,
University College Dublin, Belfield, Dublin 4, Ireland
amirali.farokhniaee@ucd.ie

Affiliations: A Farokhniaee and M. M. Lowery are with the School of Electrical and Electronic Engineering, University College Dublin, Ireland. (e-mail: amirali.farokhniaee@ucd.ie, madeleine.lowery@ucd.ie).

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Abstract

Exaggerated beta oscillations (~13-30 Hz) observed in the cortical areas of the brain is one of the characteristics of disrupted information flow in the primary motor cortex in Parkinson's disease (PD). However, the mechanism underlying the generation of these enhanced beta rhythms remains unclear. The thalamo-cortex microcircuit (TCM) contains reciprocal synaptic connections that generate low frequency oscillations in the microcircuit in healthy conditions. Recent studies suggest that alterations in synaptic connections both within and between the cortex and thalamus play a critical role in the generation of pathological beta rhythms in PD. In this study, we examine this hypothesis in a spiking neuronal network model of the TCM. The model is compared and validated against neural firing patterns recorded in rodent models of PD from the literature.

Introduction

Rhythmic oscillations can be produced by large ensembles of synchronized neurons within the brain. Their disruption can shift brain function from a healthy physiological regime to a pathological one [1]. Changes in oscillatory neural activity are strongly associated with neurological disorders such as Parkinson's Disease (PD) which affects motor function [2]. Among commonly observed activity patterns in the brain, beta band rhythms (~13 to 30 Hz), are seen to be disrupted and their power is exaggerated in PD. This is observed consistently across MEG, EEG, LFP and ECoG recordings from the motor cortex [2-4]. While it is known that motor commands originate in the motor cortex, the influence of the thalamus and basal ganglia subcortical structures on cortical information processing within the cortico-basal gangliathalamocortical (CBGTC) loop in healthy and PD states, is not well understood. Though the functional significance of exaggerated beta oscillations in PD is not yet known, it has been proposed as a potential biomarker of disrupted information flow within the motor cortex and surrounding networks. The origin and network level mechanism responsible for the generation of these beta rhythms in the motor cortex remains under discussion, with several different hypotheses proposed [4,5].

It has been suggested that the cortical beta rhythm is due to the entrainment of cortical activity originating in basal ganglia and thalamic structures. Alternatively, beta rhythms may be generated within the neocortex due to internal dynamics. An intermediate view hypothesizes that beta emerges in the neocortex, but its continuance depends on synaptic drive from basal ganglia or thalamus.

Consistent with this last hypothesis, using dynamic causal modelling, in combination with a neural mass model of the thalamo-cortical circuit, a recent study [4] has identified alterations in synaptic coupling strength within and between the motor cortex and thalamus, which can account for the generation of the exaggerated beta activity observed in the parkinsonian rat [3]. While neural mass models enable us to predict spatio-temporal patterns of neuronal activity, they do not capture single neuron activity in the neuronal populations and are not able to reproduce specific spiking patterns such as bursting, a characteristic feature of cortico-basal ganglia neural activity in PD.

The aim of this study was, therefore, to generate a spiking neuronal network of the Thalamo-Cortex Microcircuit (TCM), that allows direct comparison with neural firing patterns and LFPs recorded experimentally [3]. This work presents a spiking network model consistent with the neural mass thalamocortical model identified in the study by Reis et al., [4].

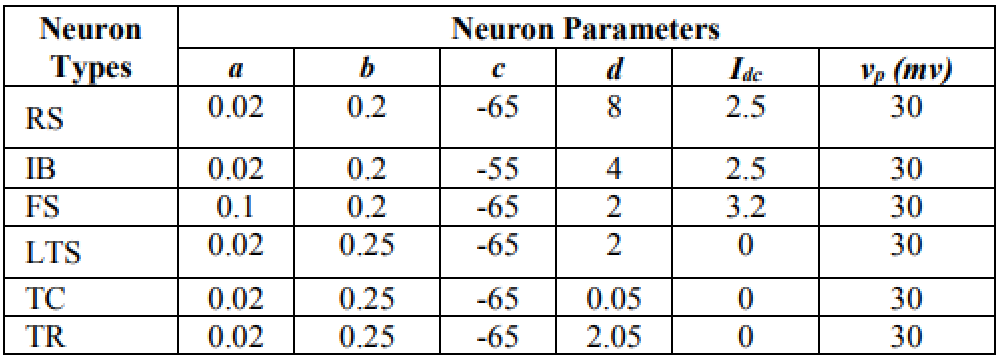
Materials & Methods

The neuronal network model of the TCM is based upon two distinct models of the motor cortex [6] and the thalamus [7]. The model is used to test the circuit features, specifically changes in coupling within and between thalamus and cortex identified by Reis et al. [4], which leads to the generation of cortical beta oscillations. Our TCM model consists of populations of excitatory and inhibitory point-like spiking neurons in the motor cortex and thalamus. The excitatory neurons in the motor cortex were divided into 3 layers of pyramidal neurons (PN), surface (S), Middle (M) and Deep (D). The inhibitory neurons in the motor cortex were considered as a single population of cortical interneurons (CI). The excitatory neurons in the thalamus formed the thalamocortical relay nucleus (TCR) and the inhibitory neurons comprised the thalamic reticular nucleus (TRN), Fig. 1A.

A. The Spiking Network Model of TCM

The spiking network model was constructed from 540 point-like neurons [8] connected via Tsodyks-Markram synapses [9, 13]. The firing rate and behavior of individual neurons are governed by parameters a, b, c and d along with a direct current (Idc) added to the transmembrane potential and a peak voltage (vp) that sets the highest value of action potentials. PN parameters in the cortex were set to generate regular spiking (RS) and intrinsically bursting (IB) behavior. CIs were subdivided into fast spiking (FS) and low-threshold spiking (LTS) neurons. All neuron parameters are given in Table I [8,10].

Table 1: Neuron Parameters



Neuron Types	Neuron Parameters					
	a	***b***	***c***	***d***	I_{dc}	v_p ***(mv)***
RS	0.02	0.2	-65	8	2.5	30
IB	0.02	0.2	-55	4	2.5	30
FS	0.1	0.2	-65	2	3.2	30
LTS	0.02	0.25	-65	2	0	30
TC	0.02	0.25	-65	0.05	0	30
TR	0.02	0.25	-65	2.05	0	30

The neuron parameters *a, b, c* and *d* were adjusted slightly for each neuron to present a level of diversity across each population [8]. For excitatory neurons with index *i*,

$(a_i, b_i) = (a, b)$

and

$(ci, di) = (c, d) + (15, -6)r_i^2$

where r is a uniformly distributed random number between 0 and 1. The fixed parameters a, b, c and d belong to each excitatory population given in Table I. For inhibitory neurons,

$(ai, bi) = (a, b) + (0.08, -0.05)r_i$

and

$(ci, di) = (c, d)$

where the parameters a, b, c and d belong to inhibitory populations.

B. Synaptic Inputs

The synaptic connections between the neurons in the network model were considered as a combination of Facilitating (F), Depressing (D) and Pseudo-linear (P) synapses with a distribution of 8% F, 75% D and 15% P [10- 12], except for the connections between layer D of the cortex and thalamus that were considered pure facilitating and between TCR and layer D which were pure depressing [7].

C. Network Connections

The parameters of the individual neurons and synaptic connection weights were set according to subthreshold dynamics, such that when populations were connected together, this leads to spontaneous firing rates of approximately <10 Hz for PN and ~8-45 Hz for Cl neurons, compatible with the reported observations and experimental recordings from layer 5 LFP of cortex in rats [3]. Two corticothalamic projection from D to TCR and TRN were considered to model the synaptic connection between the cortex and the thalamus. Reciprocally, two thalamocortical extrinsic synaptic connections were included from TCR to both D and CI [7]. There is no connection between TC neurons within TCR and all to all connection exist for TR neurons in TRN [7].

Although the thalamus projects to all layers of the cortex with different synaptic weights, we focus here on the connections identified as contributing to the generation of beta rhythms in the TCM [4]. The topology (structure) and the alterations in strength of those connections that best explain the transition from low to high beta rhythm have been identified by Reis et al. [4], utilizing fixed-effect Bayesian model comparison inference. The specific changes identified are 1) an increase in the synaptic weight of the thalamic projections from TCR to D and CI, similarly from M to S and from TCR to TRN; 2) a decrease in the synaptic coupling between S to M in the cortex, between D to both nuclei of TCR and TRN and from TRN o TCR. These changes are summarized in Figs. 1B and C.

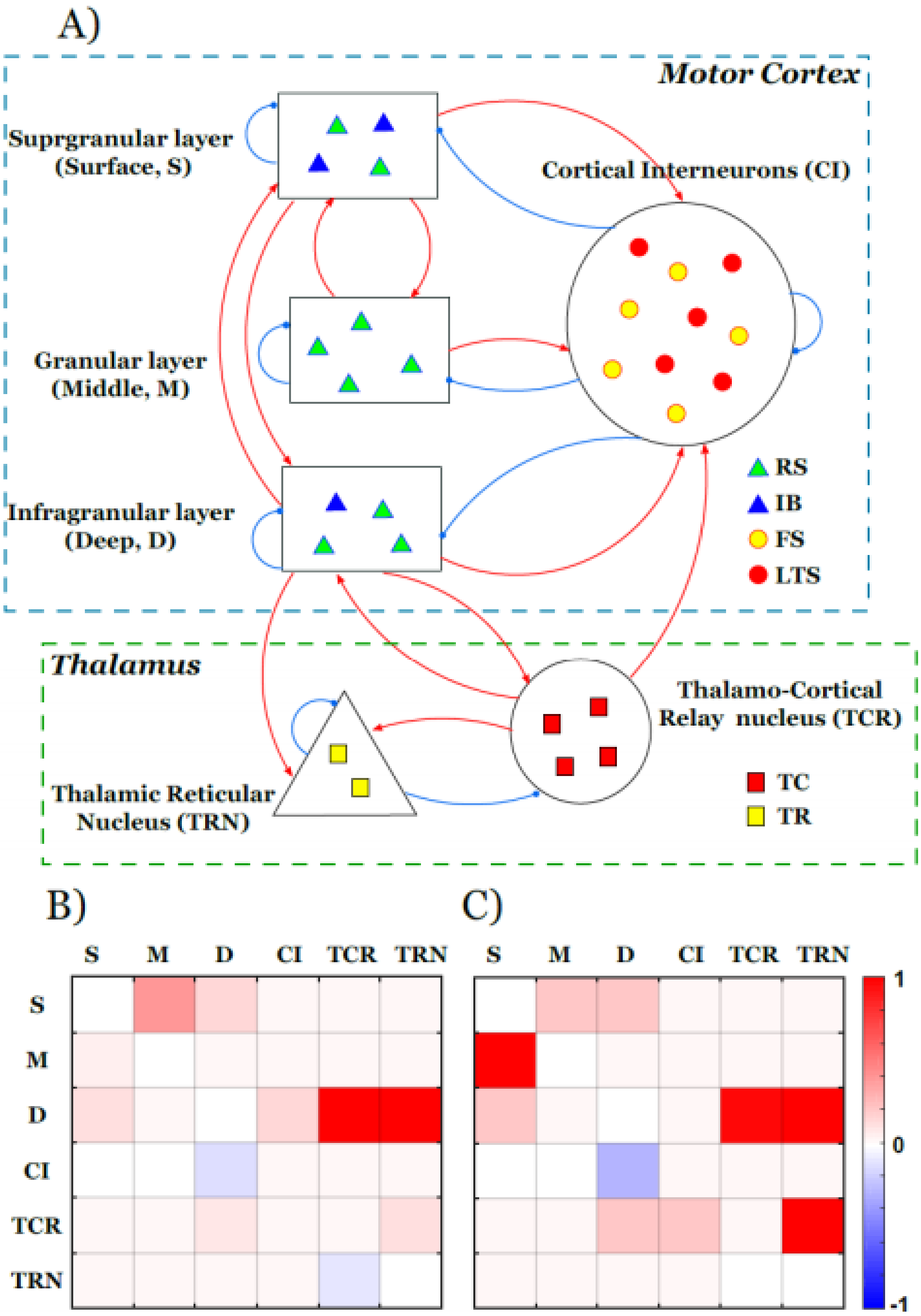


Figure 1. A) A schematic diagram of the TCM structures and connections. Each population contains 100 Izhikevich neurons (except TRN with 40 neurons) that their parameters are set to generate realistic firing patterns based on the anatomical and physiological studies up to date. The synaptic coupling between all neurons are not shown, instead the connecting curves indicate which populations are connected via excitatory (red arrows) and inhibitory (blue lines with filled circles) synapses in general. There are random all to all connections between the

neurons within all structures except TCR. B) Connectivity matrix of the normalized mean synaptic weights between structures in healthy condition. C) The same as B but for PD condition. The changes in connectivity matrix elements from B to C are compatible with the identified alterations by Reis et al. to generate beta rhythm in motor cortex [4].

The model contains directly added white Gaussian noise to individual neurons transmembrane potentials and also to their threshold potentials. Also, we weakly added postsynaptic currents that are generated by a Poissonian process with mean frequency of 15 Hz to the 3 layers of the motor cortex, mimicking spike invasions of the supplementary and premotor cortices to the primary motor cortex. Both synaptic and axonal transmission delay were considered in our TCM model. A synaptic transmission time delay of 1 ms was set along all synapses in the microcircuit. The postsynaptic currents transmission delay is 8 ms between different structures within the motor cortex and thalamus, and 1 ms within each structure [4]. The transmission delay from layer D of the cortex to thalamus (corticothalamic delay) was set to 15 ms while the opposite path (thalamocortical delay) was equal to 20 ms [14]. For further verification of the model with recent experimental recordings [3], cortical LFPs were simulated as the sum of all excitatory post-synaptic currents within layer D plus the cortical inhibitory post-synaptic currents. Simulations were conducted for 10 s epochs, with 0.1 ms time step.

Results

Simulation of the TCM activity with two different connectivity patterns (Fig. 1 B and C) resulted in a transition from low to high beta rhythm in the primary motor cortex LFP, corresponding to healthy and PD conditions. Figs. 2 and 3 illustrate the firing patterns of the TCM individual neurons and the calculated LFP of layer D of cortex (raw and filtered in beta frequency band) along with their corresponding normalized power spectrum densities for the two states of healthy and PD conditions. The spectrograms of the raw LFP were also computed in the two states. In addition, pairwise linear cross-correlations of 10 randomly chosen neurons within layer D of the motor cortex are presented as a measure of synchronization for the two states of healthy and PD.

Fig. 2A illustrates firing times of all neurons in different structures of TCM as raster plots. The spontaneous activity of TCM is evident as confirmed by the pairwise cross correlation between 10 randomly chosen PNs of layer D, Fig. 2F. To check the frequency content of these signals the normalized power spectrum density was calculated, Fig. 2C and D for the raw and beta band filtered LFP, respectively. The spectrogram shown in Fig. 2E demonstrates no consistent dominant frequency within beta band over the time course of the simulation.

An enhanced synchrony among the populations of neurons in the TCM under PD conditions is evident in the raster plot shown in Fig. 3A., confirmed by the crosscorrelation analysis between 10 random pairs of neurons in layer D (Fig. 3F). The correlation index is increased compared with the normal situation in Fig. 2F. This synchronization enhancement between firing times of the PNs in layer D and production of approximately 0.3 Hz entrained firings evident in the raster plot are consistent with the reported experimental recordings and analyses from rats [3]. Examination of the power spectrum of the LFP shows the emergence of oscillatory activity at the beta band in PD conditions (Fig. 3D) compared with the normal state.

Discussion

A new spiking neuronal network model of the TCM is presented that generates high beta rhythm in the primary motor cortex under a certain transition of synaptic couplings

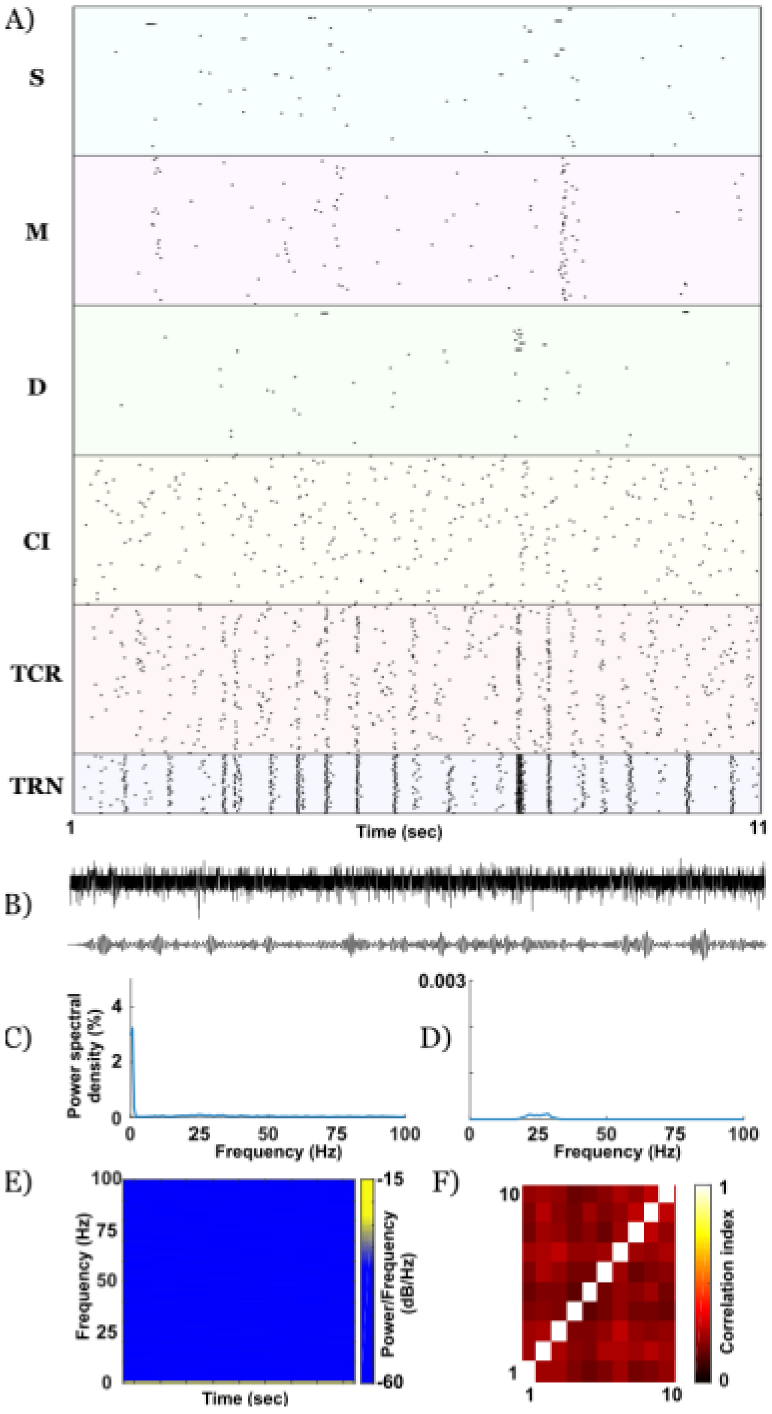


Figure 2. Simulation results in normal conditions. The network connectivity is based on the normalized mean synaptic couplings given in Fig. 1B. A) Firing patterns of different structures of TCM for 10 seconds of simulation. B) LFP evaluated as the excitatory postsynaptic currents of PNs in layer D of the motor cortex plus the inhibitory postsynaptic currents of the CI neurons (upper trace). The bottom trace shows the filtered LFP between 15-30 Hz. C and D) Normalized power spectral density of the LFP and filtered LFP, respectively. No significant beta rhythms can be observed. E) Spectrogram of the LFP shows no significant power in beta domain. F)

Pair-wise cross correlation between 10 randomly chosen PNs within layer D shows low amount of synchrony between them (correlation indices are close to zero).

within the TCM. Our results confirm the hypothesis that altering both external and internal synaptic inputs in motor cortex lead to higher beta rhythms in a spiking network

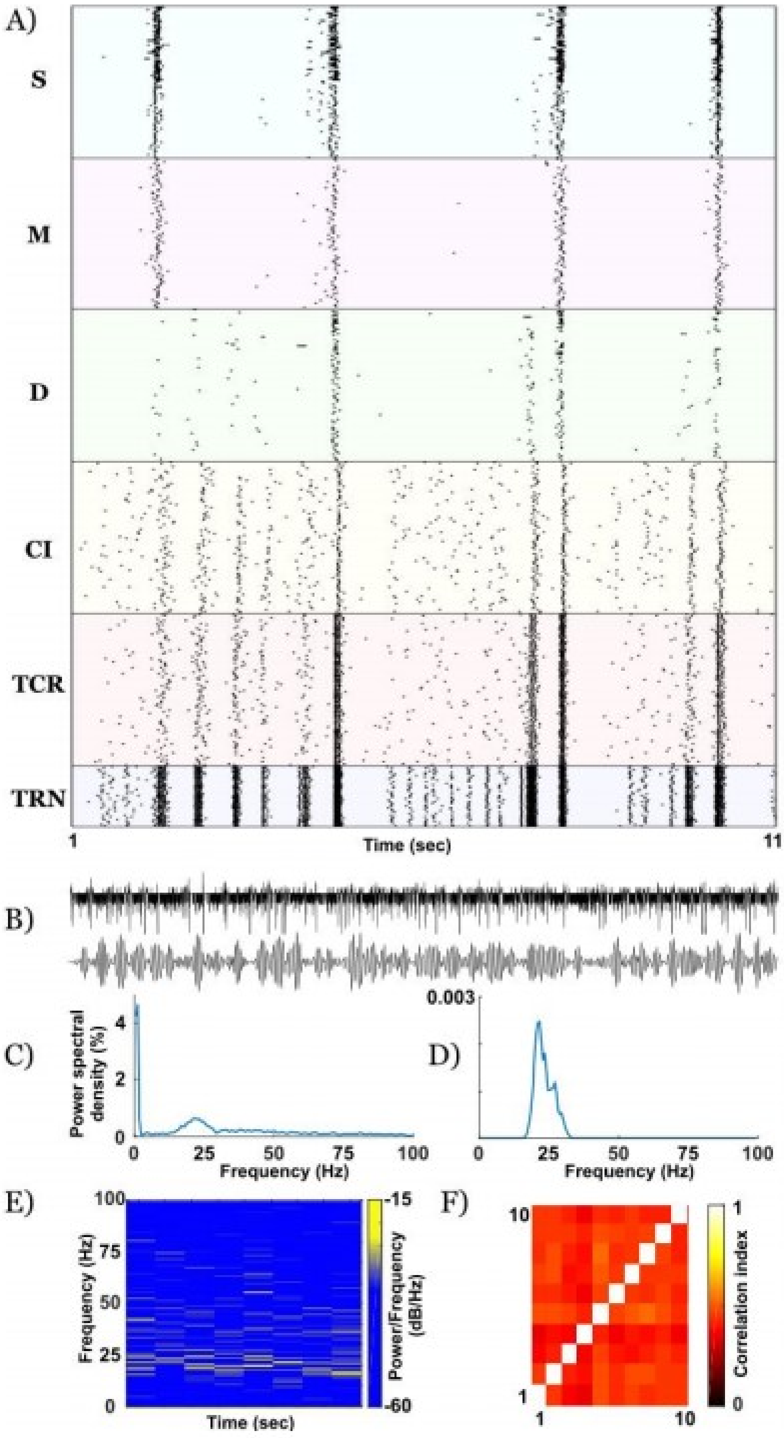


Figure 3. Simulation results in PD conditions. The network connectivity is based on the normalized mean synaptic couplings given in Fig. 1C. A) Firing patterns of different structures of TCM. B) LFP evaluated as the excitatory postsynaptic currents of PNs in layer D of the motor cortex plus the inhibitory postsynaptic currents of the CI neurons (upper trace). The bottom trace shows the filtered LFP between 15-30 Hz. C and D) Normalized power spectral density of the LFP and filtered LFP, respectively. An elevated beta rhythm is obvious in these diagrams compared with the ones in normal state (Fig. 2 C and D). E) Spectrogram of the LFP shows a consistent significant power in beta domain. F) Pair-wise cross correlation between 10 randomly chosen PNs within layer D shows higher amount of synchrony relative to the normal conditions (Fig. 2F).

model with comparable circuit mechanisms similar to recent studies [4-5]. Furthermore, the model reproduces the neural firing times of the deep layers of motor cortex along with an increased level of synchronization under PD conditions. The model supports the suggestions that the thalmocortical and corticotalamic connections, as well as coupling changes between granular and supragranular layers of the motor cortex itself, may have a functional role in generation of beta rhythms in the motor cortex. Thalamic neural activity is seen to have crucial circuit feature in this beta rhythm generation and its elevation during PD. Based on these results we propose that the beta events in the LFP are integrated over all the bursting post synaptic drives to PNs in the motor cortex. These drives last a period of beta oscillation (~33-77 ms). In addition, the beta rhythm occurred robustly in the LFP computed from the deep layer of cortex, arising from a mix of IB burst firings mixed with single action potentials and occasional bursting of RS neurons located in that layer. Note that spiking network models are difficult to implement since they involve numerous parameters to be tuned, which serves as their most important limitation that requires special attention during their validation.

In summary, the model of TCM provides a physiologically-based model of beta rhythm generation in the cortical network, which can be combined with models of the CGBTC loop to provide insights into the role of beta oscillations in neural control of movement.

References

[1] Menendez de la Prida, “Oscillations and brain function: setting the neuronal tempo in health and disease,” In Meeting of the Society for Neuroscience, Chicago, 21 October 2009.

[2] J. Modolo et al., “Model-driven therapeutic treatment of neurological disorders: Reshaping brain rhythms with neuromodulation,” Interface Focus, vol. 1, no. 1, pp. 61–74, 2011.

[3] Q. Li et al., “Therapeutic Deep Brain Stimulation in Parkinsonian Rats Directly Influences Motor Cortex,” Neuron, vol. 76, pp. 1030– 1041, 2012.

[4] C. Reis et al., “Thalamocortical dynamics underlying spontaneous transitions in beta power in Parkinsonism,” NeuroImage, vol. 193, pp. 103-114, 2019.

[5] M. A. Sherman et al., “Neural mechanisms of transient neocortical beta rhythms: Converging evidence from humans, computational modeling, monkeys, and mice,” Proc. Natl. Acad. Sci., pp. E4885– E4894, 2016.

[6] M. B. Bhatt et al., “Computational modelling of movement-related beta-oscillatory dynamics in human motor cortex,” Neuroimage, vol. 133, pp. 224–232, 2016.

[7] Shepherd GM, Grillner S, eds. “Handbook of Brain Microcircuits,” 2nd ed. Oxford, UK: Oxford University Press; 2018, pp. 99–108.

[8] E. M. Izhikevich, “Simple model of spiking neurons,” IEEE Trans. Neural Networks, vol. 14, no. 6, pp. 1569–1572, 2003.

[9] M. V. Tsodyks and H. Markram, “The neural code between neocortical pyramidal neurons depends on neurotransmitter release probability,” Proc. Natl. Acad. Sci., vol. 94, no. 2, pp. 719–723, 1997.

[10] S. E. Chelian and N. Srinivasa, “A spiking thalamus model for form and motion processing of images,” Proc. Int. Jt. Conf. Neural Networks, August 2013.

[11] H. Markram, Y. Wang, and M. Tsodyks, “Differential signaling via the same axon of neocortical pyramidal neurons,” Proc Natl Acad Sci U S A, vol. 95, no. 9, p. 5323–8., 1998.

[12] Y. Wang et al., “Heterogeneity in the pyramidal network of the medial prefrontal cortex,” Nat. Neurosci., vol. 9, no. 4, pp. 534–542, 2006.

[13] H. Markram et al., “Reconstruction and Simulation of Neocortical Microcircuitry,” Cell, vol. 163, no. 2, pp. 456–492, 2015.

[14] M. Hashemi et al., “Anesthetic action on the transmission delay between cortex and thalamus explains the beta-buzz observed under propofol anesthesia,” PLoS ONE, vol. 12, no. 6, pp. 1–29, 2017.

252