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The Role of Propriospinal Neuronal Network in Transmitting the Alternating Muscular Activities of Flexor and Extensor in Parkinsonian Tremor*

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***Abstract*—It has been shown that normal cyclic movement of human arm and resting limb tremor in Parkinson's disease (PD) are associated with the oscillatory neuronal activities in different cerebral networks, which are transmitted to the antagonistic muscles via the same spinal pathway. There are mono-synaptic and multi-synaptic corticospinal pathways for conveying motor commands. This study investigates the plausible role of propriospinal neuronal (PN) network in the C3-C4 levels in multi-synaptic transmission of cortical commands for oscillatory movements. A PN network model is constructed based on known neurophysiological connections, and is hypothesized to achieve the conversion of cortical oscillations into alternating antagonistic muscle bursts. Simulations performed with a virtual arm (VA) model indicate that without the PN network, the alternating bursts of antagonistic muscle EMG could not be reliably generated, whereas with the PN network, the alternating pattern of bursts were naturally displayed in the three pairs of antagonist muscles. Thus, it is suggested that oscillations in the primary motor cortex (M1) of single and double tremor frequencies are processed at the PN network to compute the alternating burst pattern in the flexor and extensor muscles.**

Keywords: corticospinal transmission, propriospinal neuron (PN), Parkinsonian tremor, oscillatory movements, γ dynamic control, Computational models

I. Introduction

Resting tremor in Parkinson's disease (PD) that is elicited by the activities of antagonistic muscles has reciprocal and alternating patterns [1]. The tremor of variable frequency between 3 and 7 Hz is originated from oscillatory neuronal activity in subcortical and cortical networks [2, 3]. The electroencephalography (EEG)-electromyography (EMG) [4, 5], magnetoencephalography (MEG)-EMG [6-8] and local field potential (LFP) (in subthalamic nucleus)-EMG [9] studies revealed that the peripheral EMG showed strong coupling with the neuronal oscillatory activity in brain at single tremor frequency around 5 Hz and double tremor frequency around 10 Hz. It was pointed out that these two oscillation sources possibly involve different cerebral networks and different pathways to the periphery, and the oscillatory activity of brain at double tremor frequency was the main central drive contributing to cortico-muscular coupling [11]. However, the spinal mechanism remains unknown with regard to how the 10 Hz cerebral oscillation is transformed into the alternating pattern of antagonistic muscle bursts that generate the 5 Hz tremor.

The PN network that is located in C3-C4 levels of the cervical spine has been demonstrated and described by physiological experiments in cats and macaque monkeys [12, 13], and implicated in human by electrophysiological studies [12, 14]. The studies in cats and primates have shown that the PNs are subject to multiple excitatory and inhibitory controls by cortical inputs, and the PN network is involved in reaching movement control [13]. Other simulation studies suggested that those PNs may function to coordinate control of individual muscles [15].

Based on MEG and simultaneous EMG recordings [7, 10], Timmermann and his colleagues assumed that the spinal circuitry was responsible to divide the primary motor cortex (M1) outputs into the bursting antagonistic activities [8, 11]. In this study, we further hypothesize that the PN network in the C3-C4 plays the computational role in translating cortical drives into the alternative activities of flexor and extensor muscles in the generation of Parkinsonian tremor and in normal oscillatory movements as well.

II. Model of the Propriospinal Neuronal Network

The PN network of a pair of antagonistic muscles for movement control was presented in Fig.1A based on experimentally identified physiological connections of the propriospinal neurons (PNs) [12-14]. Both mono-synaptic pathway and multi-synaptic pathway via PNs from the motor cortex to forelimb motor neurons (MNs) have been found in the cat, monkey and human [16]. PNs receive monosynaptic excitation and feed-forward inhibition (γ_d, inhibition gain for flexor/extensor is denoted as de/df) from descending tracts and feedback inhibition from forelimb afferents (Ia-PN reflex gain for flexor/extensor is denoted as af/ae). The PNs project to MNs and the interneurons mediating reciprocal Ia inhibition with a gain for flexor/extensor as pe/pf (Fig.1A).

Previous analyses of cerebro-muscular and cortico-cortical coherence in Parkinsonian resting tremor indicate that the double tremor frequency is not the harmonic component of the single tremor signal. Rather, the double tremor frequency arises from separate neuronal circuits in the brain [5, 8, and 11]. Using the dynamic imaging of coherent sources (DICS), it is found that the source of single tremor frequency is located

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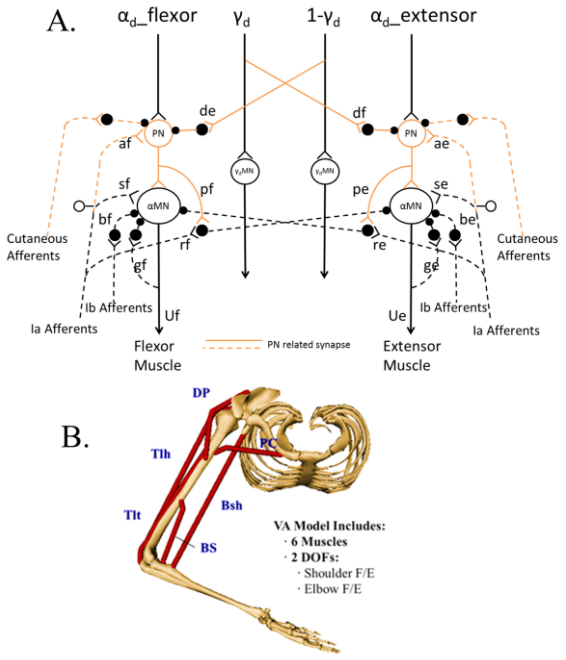

Figure 1. A). The model of PN network in descending cortico-muscular pathways of a pair of antagonistic muscles based on experimentally identified PN connections. Spinal reflex circuitry regulates the outputs of α motoneurons to muscle. B). The VA model with 6 muscles and 2 DOFs.

close to the frontal midline, and the source of double tremor frequency lies in the premotor and sensory motor cortex [4]. Thus, these two oscillations involve different brain areas, and are projected to the periphery via separate descending pathways.

In this study, we assume that the descending command of double tremor frequency projects to PNs by way of monosynaptic excitation, which is denoted as α dynamic (α_d). The outputs of PN are then projected to α motoneuron pools as driving commands of muscles. In addition, the descending command of single tremor frequency is assumed as the reciprocal feedforward inhibition projecting to PNs. This cortical inhibition serves as a mirror-gating signal at the PNs for the α_d, such that a pair of pulses in the excitatory command is channeled to flexor and extensor respectively, thus, dividing the α_d command of double tremor frequency into the alternative bursting of flexor and extensor activation at single tremor frequency. According to Taylor et al. [17-19], the γ dynamic (γ_d) activity is related to the alternating control pattern during locomotion, similar to that in the Parkinsonian resting tremor in PD patients and mimicking Parkinsonian resting tremor in healthy subjects. Thus, it is further assumed that the γ_d signal is associated to the cortical command of single tremor frequency in the Parkinsonian and voluntary oscillatory movements (Fig.1A).

III. Methods and Materials

A. A closed-loop propriospinal-virtual arm (PN-VA) model

An integrated closed-loop propriospinal-virtual arm (PN-VA) model is constructed by combing the model of the PN network and the spinal reflex circuitry with the virtual arm (VA) model [20, 21]. The VA model is composed of skeleton, virtual muscle, spindle and Golgi tendon organ (GTO) proprioceptors. The PN network model [12-14, 23] is coupled with the spinal reflex circuits of α motoneurons [22, 23]. The integrated PN spinal reflex model is implemented in MATLAB/SIMULINK (Mathworks Inc., USA). The entire PN-VA model is then simulated in the MATLAB environment.

The α motoneuron pool receives both the mono-synaptic (α static denoted as α_s) and multi-synaptic (via PNs) descending excitatory commands, as well as the spinal proprioceptive feedback. The parameters of spinal reflexes related to α motoneuron are stretch reflexes gain for flexor/extensor denoted as sf/se, recurrent inhibition gain for flexor/extensor denoted as gf/ge, reciprocal inhibition gain for flexor/extensor denoted as rf/fe, and Ib reflex gain for flexor/extensor denoted as bf/be. These gains in Table I are selected to maintain stable closed-loop responses.

A generic virtual arm (VA) model [20] has been used to emulate the tremor behavior of the arm under central oscillatory inputs. In the horizontal plane, three pairs of antagonistic muscles across the shoulder and elbow joints are selected to control two degrees of freedom (DOF) of the virtual arm (Fig.1B). There are two pairs of mono-articular muscles, such as deltoid posterior (DP) and clavicular portion of pectoralis major (PC) across the shoulder, brachialis (BS) and triceps lateral head (Tlt) across the elbow, and one pair of bi-articular muscles cross both joints, biceps short head (Bsh) and triceps long head (Tlh).

B. A closed-loop virtual arm (VA-without PN) model

A closed-loop virtual arm model without PN is obtained by removing the PN network, but spinal reflex circuits remain. This model is also simulated in the MATLAB. In this case, the α motoneuron pool receives the monosynaptic cortical excitatory commands without the processing of PN network and the spinal proprioceptive feedback.

C. Stimulation experiments of pathological and voluntary mimic Parkinsonian resting tremor

A systematic procedure of simulation has been established based on the protocol of previous studies [21]. In the simulations, a set of static commands, α static (α_s) and γ static (γ_s), is used to maintain a position of the VA (see Table I); and a set of dynamic commands, α dynamic (α_d) and γ dynamic (γ_d), contributes to the generation of tremor behaviors. The dual sets of cortical commands are responsible to control arm

TABLE I. Parameter Values In Simulations

Muscle	Reflex Gains							α_s	γ_s
	g	*s*	*r*	*b*	*a*	*p*	*d*		
PC	0.2	0.2	0.1	0.1	0.2	0	1	0.25	0.6335
DP	0.2	0.2	0.1	0.1	0.2	0	1	0.275	0.5545
Bsh	0.2	0.2	0.1	0.1	0.2	0	1	0.225	0.3938
Tlh	0.2	0.2	0.1	0.1	0.2	0	1	0.275	0.6940
BS	0.2	0.2	0.1	0.1	0.2	0	1	0.21	0.6095
Tlt	0.2	0.2	0.1	0.1	0.2	0	1	0.15	0.5252

postures and oscillations respectively.

In the simulation experiments, α_d is modeled as a sinusoidal signal with double tremor frequency (8~12 Hz); and γ_d is modeled as a sinusoidal signal of single tremor frequency (4~6 Hz) with a constant bias. The range of α_d and γ_d is from 0 to 1. There is no phase shift between α_d and γ_d. The central oscillatory inputs drive each pair of antagonistic muscles independently. The frequency contents of α motoneuronal outputs (U), joint angles of elbow and shoulder obtained in simulations are analyzed with FFT, and are compared to experimental evidence.

IV. Results

Fig.2 presents the result of one simulation of VA-PN model. The central oscillations from M1 generate alternating inputs to the motoneuron pools of all three pairs of antagonistic muscles by the PN network. The outputs of PN network in turn yield alternating burst inputs to each pair of antagonistic muscles (U), which directly contributes to the alternating activation of muscles. The dominant contents of frequency in U of all muscles are 5 Hz, but there are also multiple frequency components of 10 Hz and 15 Hz in the inputs to muscles. The virtual arm shows tremor behavior of 5 Hz primarily at the elbow joint. And there is a small magnitude of oscillation of 5 Hz at the shoulder joint as well. Interestingly, higher frequency oscillations shown in muscle inputs are filtered out by musculoskeletal dynamics. This simulation captures the characteristics of pathologic and voluntary mimic Parkinsonian resting tremor of 5 Hz. The amplitude of oscillation is increased with a greater α_d.

Fig.3 shows the results of a simulation of the VA-without PN model. The same parameters and cortical drives as those in the VA-PN simulation are used. The inputs of each pair of antagonistic muscles show an in-phase co-contracting bursts. The dominant contents of frequency in U of all muscles are 10 Hz. The virtual arm does not show obvious tremor behavior at 5 Hz. With a range of amplitudes of central oscillations, the model could not produce PD-like tremor behavior consistently. Thus, without the PN network, there is always a high level of in-phase co-contraction of antagonistic muscles, which is contradictory to the pathophysiological features of Parkinsonian resting tremor.

We also performed simulations of other scenarios of central oscillations. When the γ_d is a constant signal of 0.5 and the α_d is a 10 Hz sinusoidal signal, simulation shows no oscillatory behavior in muscles and joints, suggesting that both 5 Hz and 10 Hz central oscillations are necessary to produce tremor behaviors. Different frequencies of α_d-γ_d drives produce a range of oscillation behaviors from 3 Hz to 7 Hz, which is within the frequency range of Parkinsonian resting tremor.

V. Discussion and Conclusion

In this paper, the spinal PN network is hypothesized to translate the M1 cortical oscillations into alternating bursting activities of the flexor and extensor muscles. In simulation experiments without the PN network, the alternating pattern of antagonistic bursts could not be generated reliably with a range of magnitudes of cortical oscillations. However with the PN network, the pattern of alternating antagonistic bursts could always be observed. This suggests that the cortical outputs of pathological or normal oscillatory movements are translated to the alternating activation patterns of flexor and extensor muscles via the PN network, which in turn produces the oscillatory motion of joints at the tremor frequency. The PN network achieves the computation of cortical commands via the mirror-gating inhibition mechanism. The behaviors presented in muscle activations and joint oscillations are consistent with the experimentally observed features of EMG and joint trajectories in pathologic and voluntary mimic Parkinsonian resting tremors [1, 5-10].

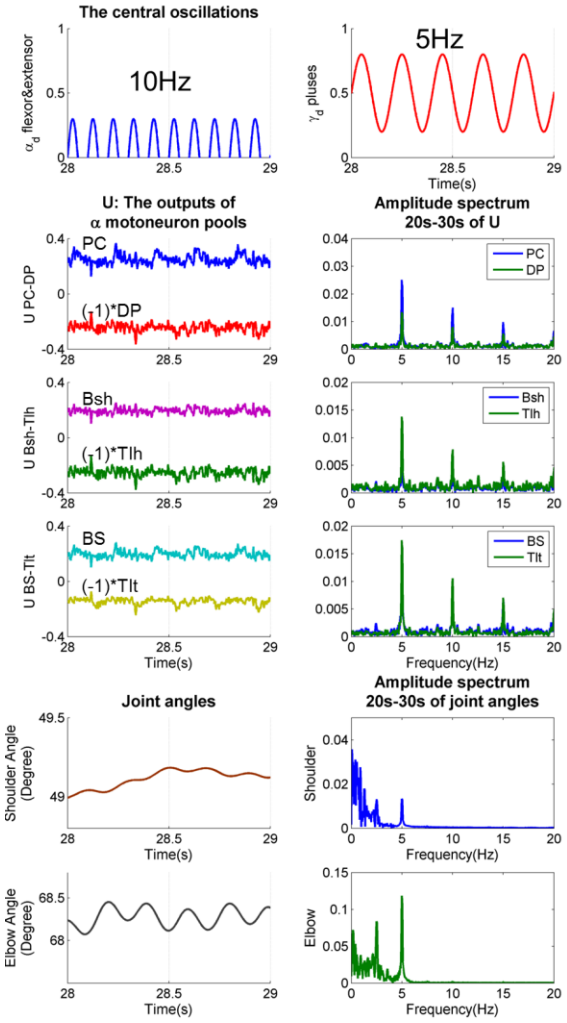

Figure 2. The results of one simulation of the VA-PN model. The central oscillations from M1, α dynamic (α_d) of double tremor frequency (10 Hz) and γ dynamic (γ_d) of single tremor frequency (5 Hz), are displayed. The outputs of α motoneuron pools of antagonistic muscles show an alternating pattern. The amplitude spectrum of U for shoulder joint and elbow muscles in the frequency domain corresponding to 20s~30s in the time domain are shown. The direct exciatations (U) to three paris of antagonistic muscles show 5 Hz and harmonic components in the frequency domain. The largest peak is at 5 Hz for all muscles. The elbow joint displayed a larger oscillation at 5 Hz than the shoulder joint.

We have also collected EMG, MEG and motion data from PD patients recently to verify the simulation results. Preliminary analysis of experiment data confirmed the

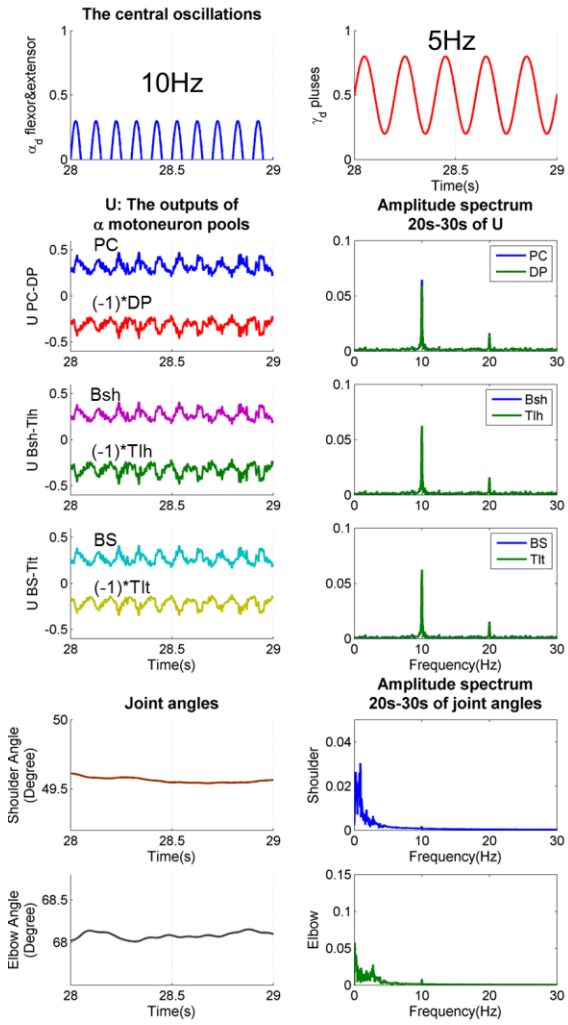

Figure 3. The results of a simulation of VA-without PN model. The U of each pair of antagonistic muscles does not show alternating patterns, but co-contracting patterns. The direct excitations (U) to three paris of antagonistic muscles show 10 Hz and harmonic components in frequency domain. There is no obvious peak at 5 Hz in amplitude spectrum both of shoulder and elbow joints.

features of Parkinsonian tremor observed with the arm rested on a horizontal plane. In addition, the PD patient was able to maintain different end-point positions with continuous tremor around the position. This appears to suggest that positional control in the cortex is separated from the commands that generate tremor. Further experiments may be designed to test the new hypothesis regarding the computation role of PN network in the genesis of Parkinsonian tremor.

The results of this study rejected the possibility that spinal reflex circuitry alone is sufficient to cause alternating flexor and extensor bursts. Instead, this study suggests a new hypothesis that the experimentally identified PN network [12-14] plays the computational role of spinal transformation of cortical oscillatory commands into the alternating pattern of control for antagonistic muscles in the generation of Parkinsonian tremor and normal oscillatory movements.

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