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Neural computational modeling reveals a major role of corticospinal gating of central oscillations in the generation of essential tremor

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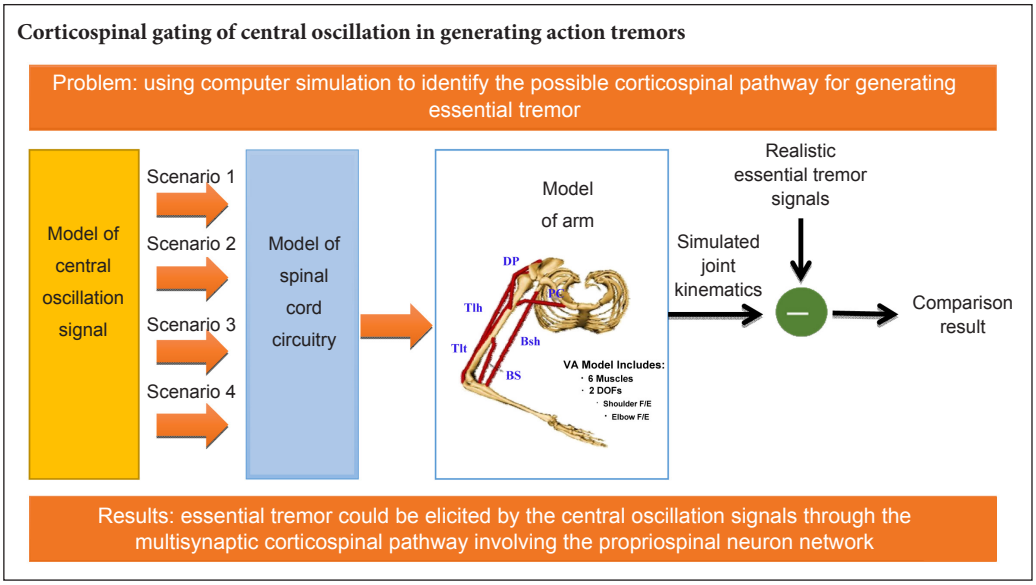
Graphical Abstract



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Abstract

Essential tremor, also referred to as familial tremor, is an autosomal dominant genetic disease and the most common movement disorder. It typically involves a postural and motor tremor of the hands, head or other part of the body. Essential tremor is driven by a central oscillation signal in the brain. However, the corticospinal mechanisms involved in the generation of essential tremor are unclear. Therefore, in this study, we used a neural computational model that includes both monosynaptic and multisynaptic corticospinal pathways interacting with a propriospinal neuronal network. A virtual arm model is driven by the central oscillation signal to simulate tremor activity behavior. Cortical descending commands are classified as alpha or gamma through monosynaptic or multisynaptic corticospinal pathways, which converge respectively on alpha or gamma motoneurons in the spinal cord. Several scenarios are evaluated based on the central oscillation signal passing down to the spinal motoneurons *via* each descending pathway. The simulated behaviors are compared with clinical essential tremor characteristics to identify the corticospinal pathways responsible for transmitting the central oscillation signal. A propriospinal neuron with strong cortical inhibition performs a gating function in the generation of essential tremor. Our results indicate that the propriospinal neuronal network is essential for relaying the central oscillation signal and the production of essential tremor.

Key Words: *nerve regeneration; neurodegeneration; essential tremor; propriospinal neurons; motoneuron; reflex; modeling; motor control; oscillation; neurological disorder; movement disorder; computational neuroscience; neural regeneration*

Introduction

Essential tremor, one of the most common neurological disorders (Louis, 2005; Zhao et al., 2011; Hallett, 2014), is often characterized as postural (Martinelli et al., 1987) and/or kinetic tremors accompanying a motor action. Both the postural and kinetic types of essential tremor typically occur in the forearm and hand with frequencies ranging from 4 to 12 Hz (Deuschl et al., 1998; Brennan et al., 2002). A strong correlation was found between the frequencies on electroencephalogram and limb electromyogram in essential tremor patients (Halliday et al., 2000; Hellwig et al., 2001, 2003; Raethjen et al., 2007; Hellriegel et al., 2012), providing insight into the pathological origin of the disorder. Essential tremor is considered to result from the activity of a single central oscillator that involves the cerebello-thalamo-cortical pathway (Pinto et al., 2003; Raethjen and Deuschl, 2012). However, the efferent pathway of the central oscillation signal (COS), from the brain to the spinal cord, and the neuronal circuits within the spinal cord involved in the generation of essential tremor remain to be identified.

An efferent pathway that could potentially convey oscillation signals for essential tremor is the propriospinal system. The involvement of propriospinal neurons in the neural control of movements has been suggested in previous studies (Isa et al., 2006; Alstermark et al., 2007), possibly indirectly *via* corticospinal projections. Although the roles of propriospinal neurons in human movement control are unclear, a realistic virtual arm model with authentic spinal neural circuits (Lan and He, 2012; He et al., 2013; Niu et al., 2017) makes it possible to test hypotheses on the role of propriospinal neurons in generating subcortical movement patterns.

A previous computational study (Hao et al., 2013) suggested that Parkinsonian tremor is transmitted from the motor cortex to the peripheral neuromuscular system through the multisynaptic corticospinal pathway, which involves the propriospinal neuronal network (Alstermark et al., 2007). The study revealed that the propriospinal neuronal network plays an important role in generating alternating tremor patterns in antagonistic muscles from central oscillations in Parkinson's disease patients. In clinical practice, essential tremor and Parkinson's disease often cause diagnostic confusion because of overlapping similarities in symptoms (Jain et al., 2006).

In this study, we used a computational model of the corticospinal virtual arm (CS-VA) with propriospinal neurons (Alstermark et al., 2007) and spinal circuitry (Mileusnic et al., 2006; Mileusnic and Loeb, 2006) to investigate the corticospinal mechanisms involved in essential tremor. Several simulation experiments were performed to investigate: (I) the corticospinal efferent pathway related to essential tremor; (II) the role of the propriospinal neuronal network in producing essential tremor; and (III) the effect of peripheral parameters, such as reflex gain, on essential tremor. We also discussed the qualitative differences between our simulation results and data from patients with essential tremor in other clinical studies (Elble et al., 1987; Britton et al., 1994; Elble et al., 1994a, b; Gao, 2004; Heroux et al., 2006; Hellwig et al., 2009; Mostile et al., 2012).

Materials and Methods

Corticospinal-virtual arm model

In our previous studies (Lan and He, 2012; He et al., 2013, 2015), we developed a computational model that simulates the movement of the human arm, and which includes details of the spinal circuitry thought to contribute to the neural control of movement. This virtual arm model successfully explains the functional significance of alpha-gamma co-activation during arm movements (Li et al., 2014, 2015). Here, we improve the original virtual arm model by adding corticospinal projections. This CS-VA model is a multiscale model which can compute central motor commands into peripheral neural signals and activate lower motor neurons (MNs) in the forelimbs of humans and other mammals. Simultaneously, the proprioceptive afferents inform the brain of the dynamic and kinematic states of the forelimbs and regulate the activation of MNs through spinal reflex circuitry. To implement these functions, the CS-VA model comprises three parts: the propriospinal neuronal network (Alstermark et al., 2007; Hao et al., 2013), spinal reflex circuitry (Mileusnic et al., 2006; Mileusnic and Loeb, 2006), and the virtual arm model (He et al., 2013) (**Figure 1**).

As shown in **Figure 1**, cortical motor commands are conveyed to α MNs through monosynaptic or multisynaptic pathways. Cortical motor commands are also delivered to γ static (γ_s, monosynaptic pathway) and γ dynamic (γ_d, multisynaptic pathway) MNs, which innervate muscle spindles. The movement commands of α dynamic MNs are integrated with the γ dynamic commands at the propriospinal neuronal network. The virtual muscles (Cheng et al., 2000) and spindles (Mileusnic et al., 2006) are activated by the outputs of α and γ MNs, respectively. The dynamic and kinematic movement trajectories are calculated using a biomechanical model of the arm. These trajectories are encoded in the primary and secondary afferents from the muscle spindles and Golgi tendon organs of the recruited muscles. The spinal reflex circuitry in **Figure 2** regulates the outputs of α MNs according to the recurrent inhibition and reflex actions provided by the I_a, I_b and I_I afferents. The spinal reflex circuitry and virtual arm subsystems are based on real physiological data (Song et al., 2008a, b), and have been verified in previous studies (Song et al., 2008a; He et al., 2013). All the component models were integrated in the SIMULINK\MATLAB (MathWorks, Natick, MA, USA) platform for simulation.

Six muscles were included in the virtual arm model, including three pairs of antagonistic muscles with two degrees of freedom. The pectoralis major (clavicle portion) and deltoid posterior were selected as the flexor and extensor of the shoulder joint, respectively. The brachialis (BS) and triceps lateral (Tlt) were selected for the elbow joint; and the biceps short head (Bsh) and triceps long head (Tlh) were selected as the bi-articular muscles (**Figure 1**).

Simulation experiment

Simulation design

Both the physiological and mechanical signals simulated by the CS-VA model were collected and analyzed. The simu-

Table 1 Details of model initiation

	PN and reflex gains							Cortical commands		
Muscles	a	d	p	r	s	g	b	α_{multi}	γ_s	γ_d
PC	0.05	1	0	0.1	0.2	0.2	0.1	0.0625	0.6335	0.5
DP	0.05	1	0	0.1	0.2	0.2	0.1	0.0688	0.5545	0.5
Bsh	0.05	1	0	0.1	0.2	0.2	0.1	0.0563	0.5618	0.5
Tlh	0.05	1	0	0.1	0.2	0.2	0.1	0.0688	0.5164	0.5
BS	0.05	1	0	0.1	0.2	0.2	0.1	0.0525	0.6095	0.5
Tlt	0.05	1	0	0.1	0.2	0.2	0.1	0.0375	0.5252	0.5

a: I_a afferent gain on PNs; d: γ dynamic inhibition gain on PNs; p: PN related reciprocal gain; r: I_a reciprocal inhibition gain; s: stretch reflex gain; g: Renshaw cell gain; b: I_b gain of Golgi tendon organ. PN: propriospinal neuron; PC: pectoralis major clavicle; DP: deltoid posterior; Bsh: biceps short head; Tlh: triceps long head; BS: brachialis; Tlt: triceps lateral.

lated data were compared with experimental data from patients with essential tremor.

We simulated a fast elbow extension movement using the CS-VA model. To focus on the origin of essential tremor, the simulation experiments were simplified into a pair of antagonistic muscles, the biceps and triceps, which controlled the elbow movement. In the simulation, the COS was considered always present. Hence, after the CS-VA was initialized and the virtual arm was in a stable resting state (see **Table 1** for details of model initiation), one of the cortical oscillating commands was used to drive the CS-VA model in different stimulation experiments. After this, a set of pulses were passed to the α multisynaptic pathway in the CS-VA model to drive the model to perform a fast elbow extension, similar to what occurs in the real world. In this movement, the virtual arm changed its elbow angle and maintained this new posture for a while after the movement.

Simulation with different central commands

Four different sources of COS were simulated to identify the one producing the most realistic essential tremor. This experiment was performed because only a few studies found a strong association between the COS and limb electromyogram within the frequency range of essential tremor (Hellwig et al., 2001, 2003; Raethjen et al., 2007). This suggests that the route from COS to muscle activity might be convoluted. The four sources of COS were the following: α in the monosynaptic pathway (α_{mono}), α in the multisynaptic pathway (α_{multi}), and γs and γ_d tracts. By matching the simulation results to the biomechanical features of essential tremor in the clinic, we should be able to identify the neural tract most likely to cause essential tremor.

α_{mono} as the COS: Evidence of direct cortico-motoneuronal connections was found in studies on the voluntary control of the hand (Lemon et al., 1998), and this pathway from the cortex is critical in controlling hand dexterity (Lemon, 2008; Isa et al., 2013). Thus, it was possible that the oscillation in the cortex was delivered through this pathway. The first set of stimulation experiments was performed using α_{mono} as the COS. In this case, the COS directly impinged on the α MN pool (**Figure 1**), which was further modulated by the spinal reflex involving I_a and I_b afferents, and by recurrent inhibition. The value of α_{multi} was set at 0. The γ_s signal, which was placed directly upon the γ MN, was at a constant value. The γ_d, which was set at a constant bias value of 0.5, was placed into the propriospinal neuronal network and on the γ MN separately. The gains of the spinal reflex were set within a range used in other published studies (Lan and He, 2012; He et al., 2013). In the simulation, a rectified sinusoid was selected to approximate the α_{mono}, at a frequency of 4–7 Hz and an amplitude of 0.1–0.5. The α_{mono} could be described as follows:

$$\alpha_{mono} = \begin{cases} A\sin(\omega t), 2k\pi \le \omega t \le (2k+1)\pi \\ 0, 2(k+1)\pi \le \omega t \le (2k+2)\pi \end{cases} \quad (1)$$

where A = 0.1, 0.2, 0.3, 0.4 and 0.5; ω = 4, 5, 6 and 7; and k = 1, 2, 3...

In the simulation experiments, formula 1 was also used for the other COSs.

α_{multi} as the COS: Two descending pathways connect the brain to the MN pool—the direct and indirect pathways. The direct pathway connects the primary motor cortex to the MN pool, and was simulated in the first simulation experiment. In contrast, the indirect pathway is a multisynaptic pathway connecting the brain to MNs *via* the propriospinal neural network. The presence of numerous indirect pathways from the brain to MNs has been shown in primates and humans (Alstermark et al., 2007; Riddle et al., 2009; Alstermark et al., 2011). These indirect pathways are mediated by intercalated neurons, such as segmental interneurons, propriospinal neurons and reticulospinal neurons. Propriospinal neurons are involved in the control of fine voluntary movements (Alstermark et al., 2011), as shown in experiments with monkeys. Hence, the COS could be transmitted through this pathway to produce essential tremor. We again chose formula 1 to approximate the COS from α_{multi}. The COS was modulated in the propriospinal neuronal network (**Figure 2**) by γ_d before impinging on the MN pool. The γ_d values used in the first simulation were also used here. The propriospinal neuronal process could be described as follows:

$$\begin{cases} P_e = \alpha_{multi}\text{-}d_e{*}\gamma_d + a_e{*}v_e \\ P_f = \alpha_{multi}\text{-}d_f{*}(1-\gamma_d) + a_f{*}v_f \end{cases} \quad (2)$$

where P_f and P_e are the propriospinal neuronal outputs to the α MN of the flexor and extensor muscles, respectively;

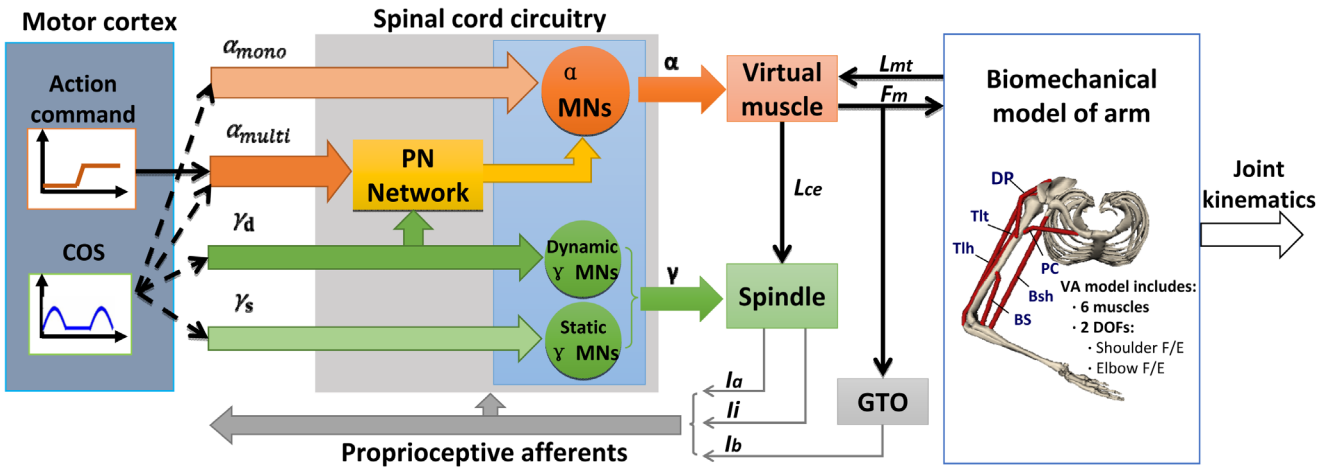

Figure 1 Corticospinal virtual arm (CS-VA) model used in this simulation study.
The CS-VA model developed in this study consists of the corticospinal pathway and the peripheral sensorimotor virtual arm. The four descending pathways are the α monosynaptic pathway from the primary motor cortex directly to the MN pool, the α multisynaptic pathway mediated by the propriospinal neuronal (PN) network, the γ dynamic pathway (γ_d), which also involves the PN network, and the γ static pathway (γ_s), which is related to postural control. An action command is added to the multisynaptic pathway to produce a movement. The central oscillation signal (COS) is sent through one of the four descending pathways to help identify the tremor generating mechanism. The sensorimotor virtual arm model, including the spinal cord circuitry, virtual muscle, proprioceptors (muscle spindle and Golgi tendon organ, GTO) and musculoskeletal dynamics, is validated to capture the realistic properties of the human upper extremity. The virtual arm has two degrees of freedom (DOF) with pairs of antagonistic muscles—pectoralis major clavicle (PC) and deltoid posterior (DP) for the shoulder, brachialis (BS) and triceps lateral (Tlt) for the elbow, and the biceps short head (Bsh) and triceps long head (Tlh) across both joints.

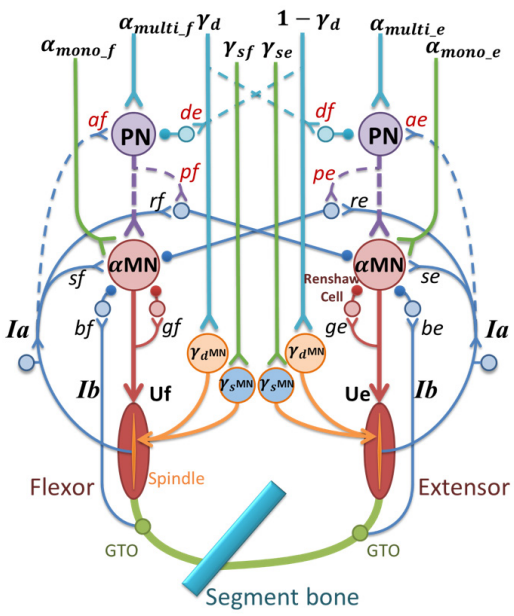

Figure 2 Model of the propriospinal neuronal (PN) network in the corticospinal pathways of one pair of antagonistic muscles.
This model is based on experimentally identified PN connections (dashed line) and spinal reflex circuitry. Subscript "d" and "s" for α and γ refer to "dynamic" and "static", respectively. "f" and "e" refer to "flexor" and "extensor", respectively. α_{multi_f} and α_{multi_e} are α signals from the multisynaptic pathway. α_{mono_f} and α_{mono_e} are α signals from the monosynaptic pathway. d_e and d_f are the inhibition gains of γ descending commands to the PN. α_f and α_e are gains of I_a to PN. P_f and P_e are the PN-related reciprocal gains. S_f and S_e are stretch reflex gains. R_f and R_e are I_a reciprocal inhibition gains. g_f and g_e are Renshaw cell gains. b_f and b_e are Golgi tendon organ (GTO) feedback gains. The outputs of GTO and spindles feedback onto the spinal cord, and are integrated with the descending and PN-processed signals to produce activating signals (U_f and U_e) that control the muscles.

α_{multi} is the α signal in the multisynaptic pathway; d_s and d_f are the inhibition of the gains of γ_d; a_e and a_f are the feedback gains of the I_a afferent onto the propriospinal neurons; and υ_e and υ_f are proportional to I_a and are afferent discharge frequencies of the spindles from the flexor and extensor muscles, respectively. The subscripts f and e are variables for the flexor and extensor muscles, respectively. This formula was obtained from a previous study (Hao et al., 2013) and was modified based on physiological evidence in other studies (Zehr et al., 2004; Zehr and Hundza, 2005; Alstermark et al., 2007; Alstermark and Isa, 2012). This model highlights the importance of spinal circuits in the modulation of muscle activity patterns.

γ_s as the COS: Both α and γ commands are known to be involved in normal voluntary movement. Based on the correlation of the behavior of these commands during midbrain stimulation with changes in the muscle spindle afferent responses to muscle stretching, the cortical γ commands were classified into two types—γ static (γ_s) and γ dynamic (γ_d) (Taylor et al., 2000). Some researchers consider γ_s to be the temporal template of the intended movement and afferent biasing through bag intrafusal fibers (Ellaway et al., 2002). According to this concept, if the COS was added to the γ_s, a tremor movement might occur. In the third simulation experiment, we used γ_s (the COS) to drive the model. This signal was directly passed onto the γ MN, similar to formula 1. In the CS-VA model, this signal could affect spindle feedback, which is the input to the α MN pool. Therefore, when the subject wants to move, tremor might result.

γ dynamic as the COS: According to previous studies (Taylor et al., 2000, 2004, 2006; Alstermark et al., 2007), γ dynamic activity is related to movement control during locomo-

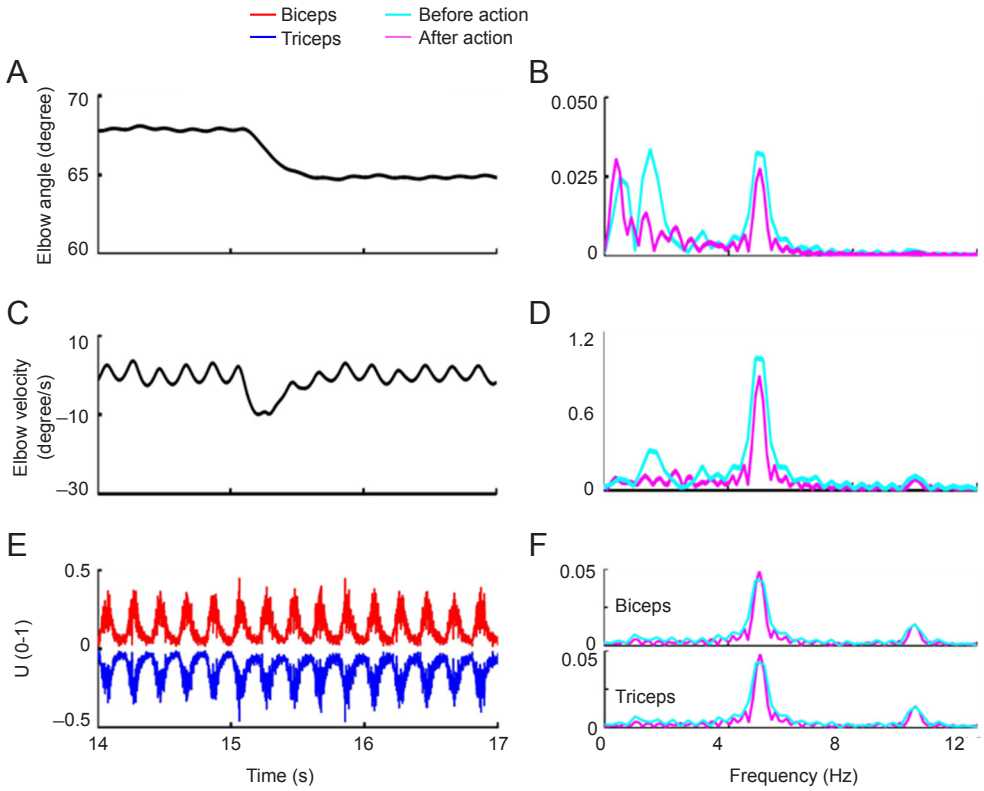

Figure 3 Features of movement and muscle activity in the simulation experiment (α_{mono}).
The figure illustrates the results of the experiment in which the central oscillation signal is the α_{mono}. The frequency of α_{mono} is 5 Hz and the amplitude is 0.3. In our design, an action occurs at 15 seconds. (A) Elbow angle traces before and after the action; (B) spectrum of this trace before and after the action; (C) the velocity of the elbow trace; (D) the spectrum of this velocity; (E) the muscle activity of the biceps and triceps before and after the movement; (F) the spectrum of the pair of antagonistic muscles before and after the action. S: Second.

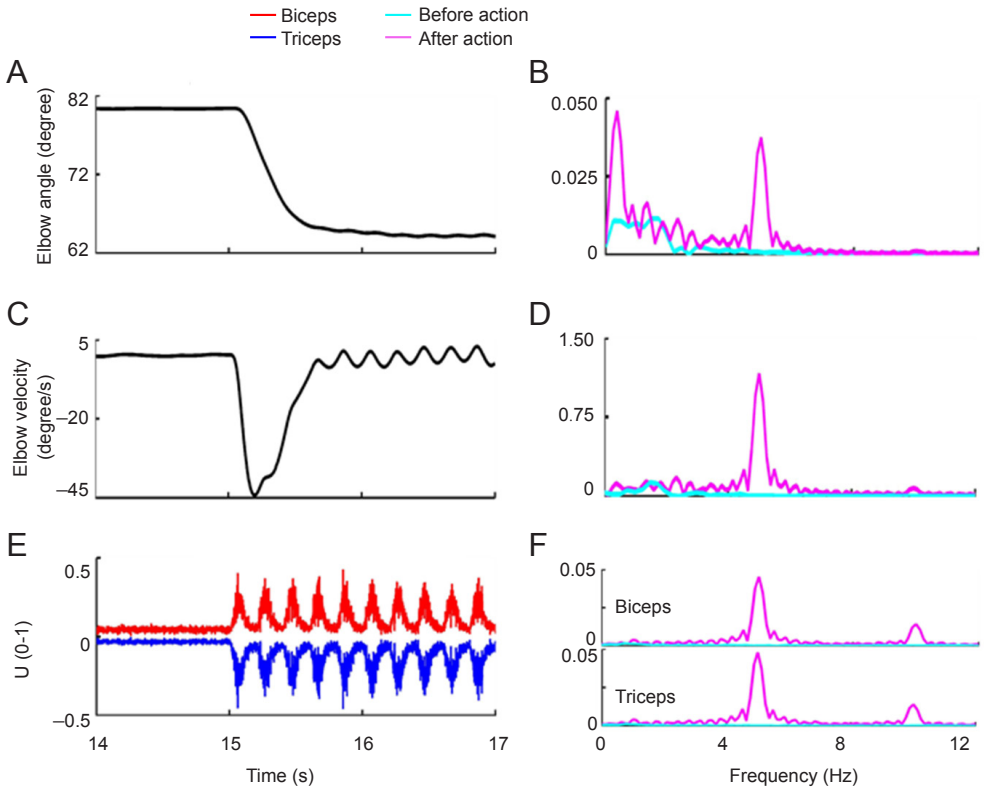

Figure 4 Features of movement and muscle activity in the simulation experiment (α_{multi}).
The figure illustrates the results of an experiment in which the central oscillation signal is the α_{multi}. The frequency of α_{multi} is 5 Hz and the amplitude is 0.3. In our design, an action occurs at 15 seconds. (A) Elbow angle traces before and after the action; (B) the spectrum of this trace before and after the action; (C) the velocity of the elbow trace; (D) the spectrum of this velocity; (E) the muscle activity of the biceps and triceps before and after the movement; (F) the spectrum of the pair of antagonistic muscles before and after the action. S: Second.

tion in decerebrated cats. These studies show that γ_d firing frequency increases unexpectedly from zero to maximum during the onset of muscle shortening, and then continues into the beginning of lengthening (Taylor et al., 2000). This observation suggests that γ_d serves an important function in movement control. Thus, γ dynamic commands might be associated with the COS at the essential tremor frequency. In the CS-VS model, similar to the second simulation, the γ_d was entered into the propriospinal neuronal network and the γ MN, but the value was a combination of the bias value of 0.5 and the rectified sinusoidal wave described in formula 1. According to formula 2, the inhibition is not a constant

value, but rather a fluctuating value. If the movement command is entered into propriospinal neurons, the abnormal γ_d can modulate the movement command in an oscillating way, affecting the α MN pool indirectly. In addition, the COS was entered into the γ MN to adjust the spindle output, which is also related to the MN pool. Hence, this might be another cause of tremor.

Simulation with different stretch reflex gains

We also examined factors that could potentially affect the amplitude and frequency of essential tremor. Based on data from essential tremor patients (Elble et al., 1994b; Matsumoto et al., 1999; Gao, 2004; Mostile et al., 2012), we proposed the following: (I) The frequency of essential tremor is only determined by the COS, as shown by corticomuscular coherence studies (Hellwig et al., 2001; Raethjen et al., 2007); and (II) The amplitude of essential tremor is related to two components, the COS and the mechanical reflex (Elble et al., 1987).

Previous studies have examined the contribution of the mechanical reflex to essential tremor by varying the inertial loading. However, obtaining accurate reflex gain values in human movements is difficult, and adjusting these values to determine a relationship between the amplitude of essential tremor and the stretch reflex is even more difficult. The main reflexes in our CS-VA model can be conveniently adjusted to determine biomechanical changes. Hence, in another set of simulations, stretch reflex gains were adjusted from 0.1 to 0.5. For each stretch reflex gain value, both the amplitude and frequency of the COS were adjusted. From the biomechanical data obtained with our model, we could quantitatively analyze the relationship between the stretch gain and the amplitude of the essential tremor.

Results

Tremor generated by the COS

With the hypothesis that the central oscillation is the originating cause of essential tremor, the abnormal joint angles and muscle behavior were calculated from the CS-VA model (plotted in **Figures 3–6**), and the spectra were analyzed. In these figures, all COSs were set at a frequency of 5 Hz and an amplitude of 0.3.

In the first experiment, α_{mono} was set as the COS pathway. Under this condition, the elbow angle always oscillated before and after the action (**Figure 3A, C**). The tremor amplitude was approximately 0.3 degree, and the amplitude decreased after the action occurred, according to the movement and velocity spectra (**Figure 3B, D**). The biceps and triceps were activated synchronously by this type of COS (**Figure 3E**), and the two muscles had nearly the same amplitude of activity during co-contraction, according to the spectral analysis (**Figure 3F, G**). The movement and velocity spectra of the elbow movement before and after the action did not show any obvious difference, contradicting the widely-held concept that essential tremor is an action tremor.

In the second experiment, α_{multi} was taken as the COS pathway. As shown in **Figure 4A**, the elbow angle did not change at the resting state, and muscle activity showed no corresponding changes (**Figure 4B**). A tremor occurred after the elbow extension. The tremor amplitude was very small, but the spectral analysis of the movement revealed the existence of two peaks, namely, one at 5 Hz and another at 1 Hz, which may have caused confusion in the observation of the tremor. However, the spectral analysis showed an obvious single peak at the tremor frequency (5 Hz) in elbow velocity after the extension movement (**Figure 4D**). The maximum value of the spectrum at 5 Hz was over 0.75, reflecting the oscillating movement. After the action, the muscle activity was in a co-contraction firing pattern of antagonistic muscles, caused by the α COS in the multisynaptic pathway. This firing pattern caused elbow oscillation, but the tremor amplitude was very small. The spectrum of the muscle activity demonstrated the co-contraction pattern at 5 Hz. The kinetic features before and after the elbow action agreed with some characteristics of essential tremor in clinical studies, and the muscle activity had a co-contraction pattern similar to the electromyogram in essential tremor patients.

In the third experiment, γ_s was taken as the initial cause of essential tremor. The commands for postural control showed an abnormal firing pattern and reached the γ MNs directly. The elbow angle showed very small tremor after the movement (**Figure 5A**). Muscle activity was enhanced after the action (**Figure 5E**), but the spectral analyses of the two muscles showed that muscle activity was neither synchronous nor alternating. In addition, the muscle activity spectra showed that there was no difference in tremor frequency, whether the arm moved or not (**Figure 5F, G**).

The last experiment used h_d as the COS. Before it reached the γ MN, d was conveyed through the propriospinal neuronal network. Similar to the second experiment, no tremor was found at resting state, and the tremor behavior was observed after the action (**Figure 6A**). Compared with the second experiment, the tremor in the elbow trace in **Figure 6A** was easily detectable because tremor amplitude was relatively high. The elbow angle oscillated between 76° and 77° at a frequency of 5 Hz, the same as the COS frequency. The biggest difference between the simulation experiments was that muscle activity showed an alternating pattern in the present simulation (**Figure 6E**). The spectra showed that muscle activity peaked at 5 Hz, the tremor frequency, in both the biceps and triceps, despite different activity levels (**Figure 6F, G**).

Influence of the oscillating parameters of COS on the simulated tremor

Our current simulation experiments indicate that α_{multi} and α_d are the COSs underlying essential tremor. We also examined the COS parameters that influence the amplitude of elbow oscillation, *i.e.* the amplitude and frequency. **Figure 7** shows the relationships between these COS parameters and the elbow oscillating amplitude. The amplitude of u_{multi} and n_d ranged from 0.1 to 0.5. The frequency of r_{multi} and α_d was adjusted from 4 to 7 Hz. Regardless of the COS (whether α_{multi} or o_d), the same regulatory effect was found—frequen-

cy had a greater impact on tremor amplitude. The lower the COS frequency, the larger the tremor amplitude. When the frequency was reduced from 4 to 5 Hz, the tremor amplitude decreased drastically. However, the tremor amplitude changed less in the range between 5 and 6 Hz. Moreover, the tremor disappeared when COS in the t_{multi} pathway was at 7 Hz. As the COS was delivered through the α_{multi} pathway, the tremor amplitude first increased along with the increase in COS amplitude from 0.1 to 0.4, and reached the maximum value when the COS amplitude was 0.4, and then decreased as COS amplitude increased from 0.4 to 0.5 (**Figure 7A**). The tremor amplitude monotonously increased when COS was w_d, as shown in **Figure 7B**. These findings show that whether the COS is from the α_{multi} or h_d pathway, the tremor frequency is determined by the frequency of the COS. COS amplitude only influences tremor amplitude.

Stretch reflex-caused oscillation contributed to essential tremor

Figure 8 shows the effect of stretch reflex gain on the amplitude. Given that the COS was from the t_{multi} pathway, with an amplitude of 0.3, the tremor amplitude was only affected by the COS frequency. Increasing stretch reflex gain did not influence tremor amplitude, as shown in **Figure 8A**. When the COS frequency was fixed at 5 Hz, and the COS amplitude was within 0.3, increasing stretch reflex gain did not affect tremor amplitude, as shown in **Figure 8B**. However, increasing stretch reflex gain reduced tremor amplitude when the COS amplitudes were 0.4 and 0.5 (**Figure 8B**). As shown in **Figure 8C**, except when the d was at 4 Hz (the w_d amplitude was maintained at 0.3), increasing stretch reflex gain weakly affected tremor amplitude, compared with the effect of t_d frequency. The amplitude of f_d and the stretch reflex gain had similar effects on the tremor amplitude (**Figure 8D**).

Discussion

In this study, a set of simulation experiments were performed to identify the efferent spinal pathway conveying the COS from the brain, and whether the propriospinal neuronal network is involved in the generation of essential tremor. In our simulation experiments, n_{mono} and α_s were excluded as the COS pathways causing essential tremor, because the kinetic and physiological characteristics did not match the clinical features of essential tremor.

Essential tremor can be classified into two types, based on clinical assessment: type A and type B (Deuschl et al., 1987; Milanov, 2001). Deuschl et al. showed that in type A essential tremor, electromyography shows synchronous activity in the antagonistic muscles, whereas electromyography shows alternating activity in the antagonists in type B essential tremor. Moreover, in Milanov's study, more than 200 essential tremor patients were recruited, and similar results were obtained. Correlating the clinical characteristics with the simulation results suggests that the tremor caused by y_{multi} is most likely the type A variety. In the second experiment, the tremor caused by COS from the α_{multi} pathway did not appear in the resting state and had low amplitude after elbow extension. These kinetic features are similar to the clinical characteristics. In addition, the muscle activity was of a co-contraction pattern. The tremor caused by the γ_d pathway COS in the simulation experiments can be identified as type B using the same method. The kinetic characteristics of the elbow and muscle activities matched the signs of type B essential tremor, with the tremor amplitude larger than in type A, with alternating muscle activity (Britton et al., 1994).

Both types of COS were modulated by the propriospinal neuronal network in the spinal cord. This shows the importance of the propriospinal neuronal network in controlling human movement. The propriospinal neuronal network, which serves a gating function, modulated the central commands from the brain to the spinal cord. Our findings could be related to observations of the corticospinal tract in patients with ET and PD (Lu et al., 2016). In terms of movement control angle, essential tremor can be identified clearly at the spinal cord level. In type A essential tremor, propriospinal neurons gate the α_{multi} COS. Indeed, essential tremor patients show no tremor in the resting state. However, when COS was added to the movement control signals, it surmounted the gating by the propriospinal neurons to reach the α MNs. This explains the occurrence of tremors when an action is performed. In type B essential tremor, the γ_d COS overcame the propriospinal neuronal gating function by lowering the gating value. At resting state, α is too small to cause tremor, even when the propriospinal neuronal gating function is impaired. When a patient wants to move or maintain a posture, and α is sufficiently large, propriospinal neuronal gating would be unable to prevent tremor.

In previous studies, we used a similar model that included the propriospinal neuronal network to simulate Parkinson's disease tremors. The simulation results matched the clinical features of Parkinson's disease tremors. Thus, the propriospinal neuronal network is involved in both tremors. Essential tremor and Parkinson's disease tremors share the same circuits in the spinal cord. Indeed, the signs of both tremors are similar and overlapping, and distinguishing them is clinically difficult.

In a previous study (Elble et al., 1987), the stretch reflex in essential tremor was examined, and the tremor was found to be influenced by two components—COS and the mechanical reflex. However, tremor frequency was determined by the central oscillation. Our current results are in agreement with these observations. COS frequency not only impacted tremor frequency, but also strongly influenced tremor amplitude in our simulation experiments, regardless of the COS pathway (f_{multi} or r_d) (**Figures 7** and **8**). An advantage of the CS-VA model, the influence of the stretch reflex gain can be directly investigated in the simulation. In type A essential tremor, the stretch reflex gain had none or little effect on the tremor amplitude, as shown in **Figure 8**. In type B essential tremor, increasing stretch reflex gain aggravated the tremor amplitude until the tremor amplitude was over 0.035. Our results provide novel insight into the neurological basis of essential tremor.

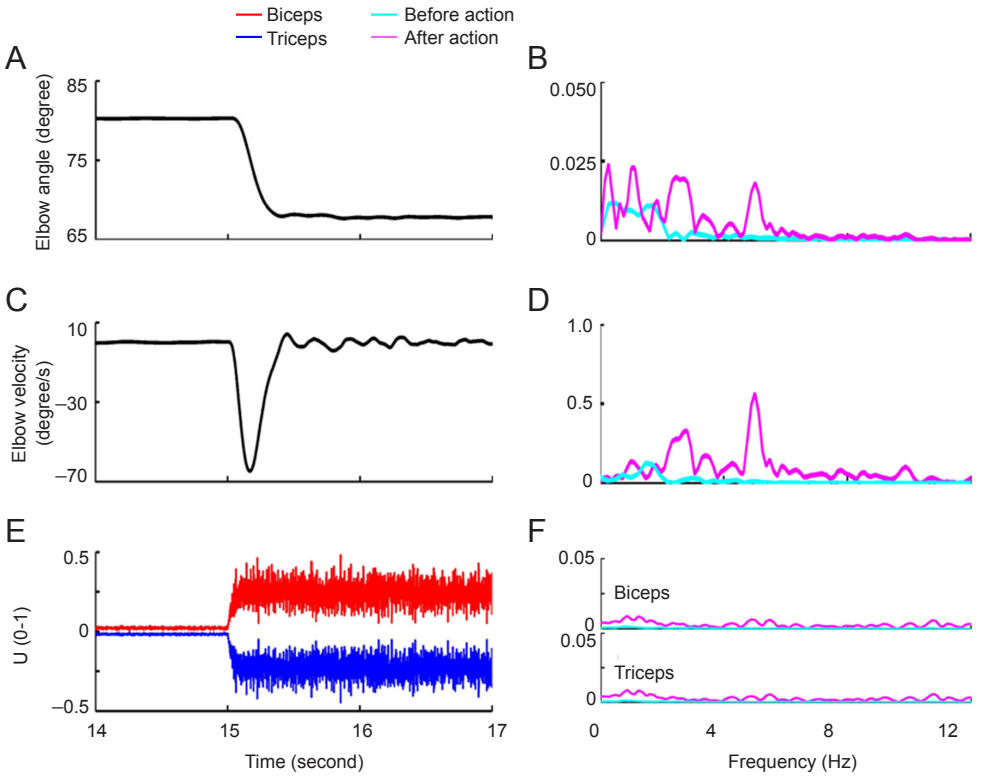

Figure 5 Features of movement and muscle activity in the simulation experiment (γ_s).
The figure illustrates the results of an experiment in which the central oscillation signal is the γ_s. The frequency of γ_s is 5 Hz and the amplitude is 0.3. In our design, an action occurs at 15 seconds. (A) Elbow angle traces before and after the action; (B) the spectrum of this trace before and after the action; (C) the velocity of the elbow trace; (D) the spectrum of this velocity; (E) the muscle activity of the biceps and triceps before and after the movement; (F) the spectrum of the pair of antagonistic muscles before and after the action.

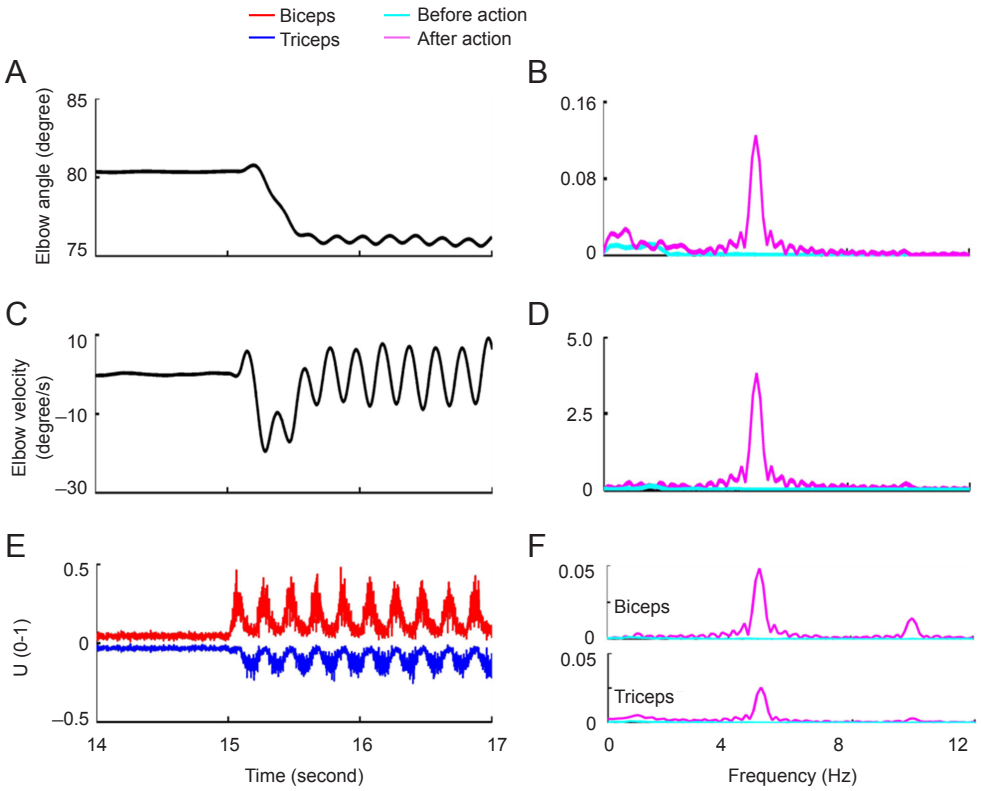

Figure 6 Features of movement and muscle activity in the simulation experiment (γ_d).
The figure illustrates the results of an experiment in which the central oscillation signal is the γ_d. The frequency of γ_d is 5 Hz and the amplitude is 0.3. In our design, an action occurs at 15 seconds. (A) Elbow angle traces before and after the action; (B) the spectrum of this trace before and after the action; (C) the velocity of the elbow trace; (D) the spectrum of this velocity; (E) the muscle activity of the biceps and triceps before and after the movement; (F) the spectrum of the pair of antagonistic muscles before and after the action.

In our study, essential tremor was elicited by the COS through the multisynaptic corticospinal pathway involving the propriospinal neuronal network. The propriospinal neuron plays an important role in gating the COS at resting state, preventing the COS from passing down to the peripheral neuromuscular system. During the performance of an active task, cortical inhibition of the propriospinal neuron is reduced or removed by task commands, and the COS can be transmitted to the peripheral neuromuscular system freely, causing a tremor activity that accompanies the task. The simulation analyses here suggest that the propriospinal neuronal network plays a role in the gating of the cortical

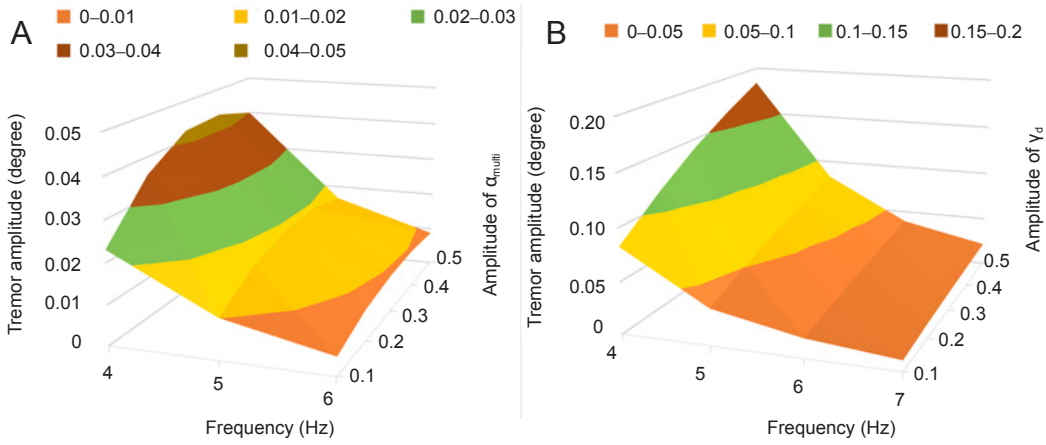

Figure 7 Influence of the frequency and amplitude of the central oscillation signal (COS) on tremor amplitude. (A) The tremor amplitude varies with frequency and the amplitude of the COS, when the COS is α_{multi}. (B) The tremor amplitude varies with frequency and amplitude of the COS, when the COS is γ_d.

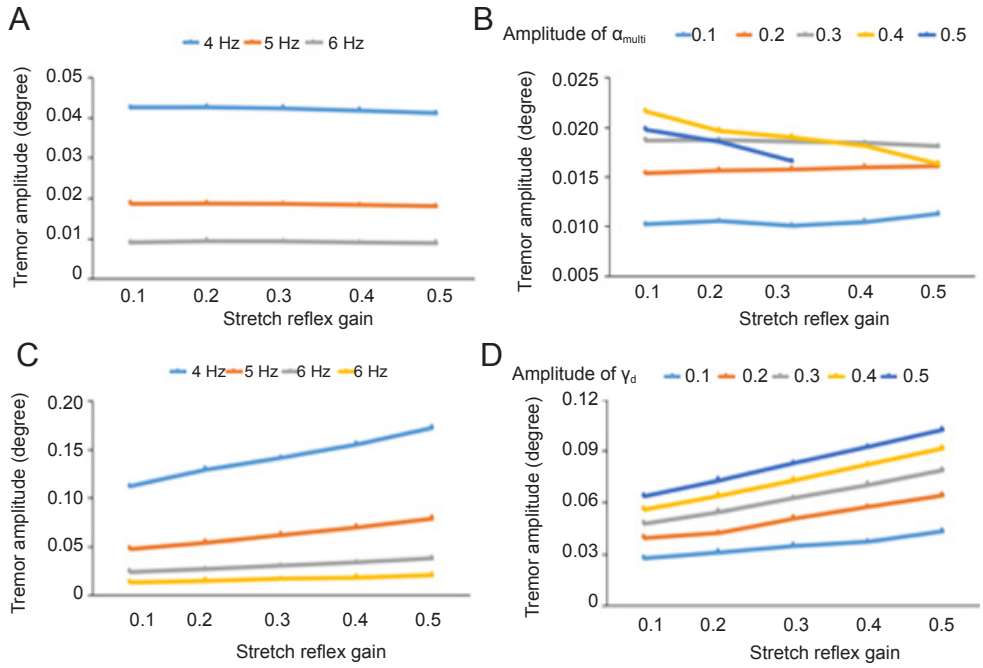

Figure 8 Relationship between tremor amplitude and reflex gain. (A, B) Relationship between tremor amplitude and reflex gain when the central oscillation signal (COS) is α_{multi}. (A) Changes in tremor amplitude when the stretch reflex gain varies from 0.1 to 0.5 at different tremor frequencies (4, 5 and 6 Hz) and the same COS amplitude of 0.3. (B) Changes in tremor amplitude when stretch reflex gain varies from 0.1 to 0.5 at different COS amplitudes and the same frequency of 5 Hz. (C, D) The relationship between tremor amplitude and reflex gain when the COS is γ_d. (C) Changes in tremor amplitude when stretch reflex gain varies from 0.1 to 0.5 at different tremor frequencies (4, 5, 6 and 7 Hz) and the same COS amplitude of 0.3. (D) Changes in tremor amplitude when stretch reflex gain varies from 0.1 to 0.5 at different COS amplitudes and the same frequency of 5 Hz.

oscillation signal, preventing it from reaching the peripheral muscles in the resting state, but allowing it to pass to the muscles during an active task.

In conclusion, COS frequency is the major factor influencing tremor amplitude, with a greater impact than COS amplitude or stretch reflex gain. Computational modeling is an effective method of simulating essential tremor and identifying abnormal neural networks.

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