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Neural mass models describing possible origin of the excessive beta oscillations correlated with Parkinsonian state

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HIGHLIGHTS

- Neural mass models simulate pathological oscillations of the basal ganglia (BG).
- The origins of upper and lower beta frequency oscillations in the BG are different.
- There is a transition mechanism between upper and lower beta oscillatory activities.
- Self-inhibition within the GPe plays a significant role.

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ABSTRACT

In Parkinson's disease, the enhanced beta rhythm is closely associated with akinesia/bradykinesia and rigidity. An increase in beta oscillations (12–35 Hz) within the basal ganglia (BG) nuclei does not proliferate throughout the cortico-basal ganglia loop in uniform fashion; rather it can be subdivided into two distinct frequency bands, i.e. the lower beta (12–20 Hz) and upper beta (21–35 Hz). A computational model of the excitatory and inhibitory neural network that focuses on the population properties is proposed to explore the mechanism underlying the pathological beta oscillations. Simulation results show several findings. The upper beta frequency in the BG originates from a high frequency cortical beta, while the emergence of exaggerated lower beta frequency in the BG depends greatly on the enhanced excitation of a reciprocal network consisting of the globus pallidus externus (GPe) and the subthalamic nucleus (STN). There is also a transition mechanism between the upper and lower beta oscillatory activities, and we explore the impact of self-inhibition within the GPe on the relationship between the upper beta and lower beta oscillations. It is shown that increased self-inhibition within the GPe contributes to increased upper beta oscillations driven by the cortical rhythm, while decrease in the self-inhibition within the GPe facilitates an enhancement of the lower beta oscillations induced by the increased excitability of the BG. This work provides an analysis for understanding the mechanism underlying pathological synchronization in neurological diseases.

1. Introduction

Parkinson's disease (PD) is a common progressive neurodegenerative disorder characterized by a profound degeneration of nigrostriatal dopaminergic neurons (Walters & Bergstrom, 2009). Such a pathological degeneration results in a decrease in the level of dopamine in the brain, which induces the occurrences of abnormal discharges in the neurons of the basal ganglia (BG) in both patients (Magnin, Morel, & Jeanmonod, 2000; Weinberger et al., 2006) and animal models (Moran et al., 2011; Wichmann, 2005) of PD. Periodic oscillatory activity is typically presented in recordings (Hutchison, 2004), which has been shown to correlate with the motor symptoms of PD, such as akinesia/bradykinesia, rigidity and tremor (Bergman & Deuschl, 2002). It is known that, akinesia/bradykinesia and rigidity are associated with oscillations in the beta-band range of frequencies (12–30 Hz) in the BG nuclei (Kuhn et al., 2008; Ray et al., 2008). In addition, there is a relationship

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between synchronous theta-band (3–10 Hz) oscillatory activity and Parkinsonian resting tremor (Tass et al., 2010).

There have been previous studies focusing on the explorations of the origins of the abnormal oscillations, especially the beta oscillations in the BG network. Some results showed that pathological beta oscillations seen in the BG could result from a periodic external drive (such as cortical input) or interactions between the excitatory and inhibitory nuclei (i.e. subthalamic nucleus (STN) and globus pallidus externus (GPe)) within the BG (Moran et al., 2011; Nevado-Holgado, Mallet, Magill, & Bogacz, 2014; Plenz & Kital, 1999). Because of the complex network interactions within the BG, computational modeling is an important tool to explore the conditions of sustained pathological oscillations that are inherent in PD (de Paor & Lowery, 2009; Holt & Netoff, 2014; Pasillas-Lépine, 2013). Gillies et al. established a computational model to capture the dynamics of the STNGPe reciprocal loop and thought the periodic rhythmic oscillations are favored by increased inhibition of the globus pallidus (GP) (Gillies, Willshaw, & Li, 2002). Holgado et al. identified a simple set of necessary conditions on model parameters that guarantee the existence of beta oscillations. They proposed that beta oscillations in the STN-GPe network could occur independently on the rhythms of the cortical inputs (Holgado, Terry, & Bogacz, 2010). Brittain et al. reviewed the different mechanisms of the lower beta (12–20 Hz) and upper beta (21–35 Hz) oscillations in the BG. It appears likely that the upper cortical beta range impacts the BG activity, while the emergence of a pronounced lower beta oscillation in the BG's local field potentials (LFPs) is due to the reciprocal structure of the excitatory and inhibitory neural network (Brittain & Brown, 2014). Thus, in order to further explore these hypotheses a computational model is used to show the contribution of the cortical external input and the intrinsic properties of the BG to the emergent pathological beta oscillation.

Recently, mesoscopic models of the BG have received increasing interest among researchers (Haidar et al., 2014; Nevado-Holgado et al., 2014; Pavlides, Hogan, & Bogacz, 2015; Pavlides, John Hogan, & Bogacz, 2012; Tsirogiannis, Tagaris, Sakas, & Nikita, 2010), which focus on the possible mechanisms for generation of excessive beta oscillations in PD. However, these models do not distinguish between lower and upper beta oscillations occurring in the pathological BG. This work uses an approach that is similar to a well-known mesoscopic cortical model developed by Jansen and Rit (1995) and Jansen, Zouridakis, and Brandt (1993), which describes the dynamical characteristics of the different rhythms. By changing the internal coupling connection within and external coupling connection to the BG from cortex and striatum from pulse densities of action potentials to the LFPs, a novel neural mass model of BG is proposed. This model may contribute to an exploration of the different mechanisms of the pathological neural oscillations at the lower and upper beta frequency bands in PD. Based on the established computational model, the roles of the neurons' excitability and self-inhibition within the GPe are investigated. The rest of this paper is organized as follows. Section 2 describes a computational model of the pathological oscillatory population dynamics. In Section 3, the possible origins of the pathological beta oscillations are explored. Finally, the conclusions are given in Section 4.

2. Model and methods

According to the anatomy of the BG (Fig. 1(a) and (b)) and electrophysiological findings in PD, a neural mass model that describes the neural population behaviors of the BG is proposed based on an original cortical model proposed by Jansen and Rit (1995) and Jansen et al. (1993), a BG model proposed by de Paor and Lowery (2009) and a cortico-basal ganglia-thalamic model proposed by Moran et al. (2011). As shown in Fig. 1(c), the excitatory nucleus STN and the inhibitory nucleus GPe are represented by sigmoidal nonlinear elements and second-order linear elements. In this classic mean field approach, the low-order dynamical linear system approximates the average neuronal membrane summation of synaptic input, and the sigmoidal nonlinear block computes the expected spike density for the population (Wilson & Cowan, 1972). The outputs of the model are the LFPs of the GPe and STN. Here, y_{Cor} represents a cortical input to the STN and y_{Str} represents an inhibitory input from the striatum to the GPe (Davidson, de Paor, & Lowery, 2014; de Paor & Lowery, 2009). It was reported that the gain of the linear element plays a significant role in changing the excitation or inhibition of the neural network (Jansen & Rit, 1995; Jansen et al., 1993; Lopes, Hoeks, Smits, & Zetterberg, 1974; Lopes, van Rotterdam, Barts, van Heusden, & Burr, 1976; Mina, Benquet, Pasnicu, Biraben, & Wendling, 2013; Wilson & Cowan, 1972).

The BG model contains a reciprocal structure in which the STN projects excitatory synaptic connections to and receives inhibitory feedback from the GPe, and the GPe also has recurrent inhibitory connections to itself. In this work, C_1, C_2 and C_3 describe the coupling strengths of the inhibitory connections from GPe to STN, the excitatory connections from STN to GPe and the self-inhibition within the GPe, respectively. Here, the coupling strength parameters are assumed to satisfy $C_1 = C_3 = 0.5C_2$, with $C_2 = 20$.

The mathematical basis of the population level formulation used in this work is derived from several previously published models (Jansen & Rit, 1995; Jansen et al., 1993; Lopes et al., 1974, 1976; Mina et al., 2013; Wilson & Cowan, 1972), although these models were originally used to describe the dynamics of the cortex. Two sigmoidal functions are used to describe the nonlinear dynamical properties of the GPe and STN (Moran et al., 2011), respectively, which are given by

$$S_{\text{GPe}}(v) = \frac{2\lambda_g}{1 + e^{-r_g v}} - \lambda_g \tag{1}$$

$$S_{\text{STN}}(v) = \frac{2\lambda_s}{1 + e^{-r_s v}} - \lambda_s \tag{2}$$

where v represents the input of the sigmoid element, i.e. the LFPs. λ_g and λ_s determine the maximum firing rate of the neural population of the GPe and STN; r_g and r_s are the slope of the sigmoid function at the origin, which may denote the effects of dopamine on the GPe and STN, respectively (Davidson et al., 2014).

The transfer functions of the second-order linear elements are given as:

$$G_{\text{GPe}}(s) = \frac{H_g \tau_g}{(\tau_g s + 1)^2} \tag{3}$$

$$G_{\text{STN}}(s) = \frac{H_s \tau_s}{(\tau_s s + 1)^2} \tag{4}$$

where $s = \sigma + j\omega$ is the Laplace variable. τ_g and τ_s represent the time constants of passive membranes in the GPe and STN. H_g and H_s are the maximum amplitudes of the GPe and STN synaptic gains, respectively, that parameterize the inhibition of the GPe and the excitability of the STN. H_g and H_s increase as dopamine is depleted.

In control theory, a transfer function is a mathematical representation to describe the relationship of the system input and output. According to the relationship between transfer function and differential equation, we can use the differential operator d/dt to replace Laplace operator s. Here dy/dt can be rewritten as $\dot{y}$ and d^2y/dt^2 can be rewritten as $\ddot{y}$. Thus, the differential equations that