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A brain network model explaining tremor in Parkinson's disease

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ABSTRACT

This paper presents a novel model of tremor in Parkinson's disease (PD) based on extensive literature review as well as novel results stemming from functional stereotactic neurosurgery for the alleviation of tremor in PD. Specifically, evidence that suggests the basal ganglia induces PD tremor via excessive inhibitory output to the thalamus and altered firing patterns which in turn generate rhythmic bursting activity of thalamic cells is presented. Then, evidence that the thalamus generates PD tremor by facilitating the generation and consolidation of rhythmic bursting activity of neurons within its nuclei is also offered. Finally, evidence that the cerebellum may modulate characteristics of PD tremor by treating it as if it was a voluntary motor behavior is presented. Accordingly, the current paper proposes that PD tremor is induced by abnormal basal ganglia activity; it is generated by the thalamus, and modulated or reinforced by the cerebellum.

Contents

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1. Introduction

Parkinson's disease (PD) is a multi-symptomatic syndrome in which almost all patients will experience tremor at a given time in the disease process (Jankovic, 2008; Deuschl et al., 1996; Rajput et al., 1991). The clinical manifestation of PD can vary; some patients will show tremor at the onset of disease, which may eventually disappear, while others will be plagued with tremor that will increase in amplitude as the disease progresses (Hughes et al., 1993). Of note, only a minority of patients will present with a true akinetic form of the disease, without any history of clinically-visible tremor (Martin et al., 1973). The tremor experienced by patients with PD will usually be present when the limb is at rest; when the hand or arm is supported, or dangling freely without muscle contraction to counteract gravity (Jankovic, 2008; Deuschl et al., 1998; Daneault et al., 2013a). This tremor at rest tends to disappear upon movement initiation, but may re-emerge once the patient has reached the endpoint of his or her movement (Jankovic et al., 1999; Duval, 2006). This re-emergent tremor may occur even though the patient maintains a muscle contraction to counteract gravity. The spectral characteristics of this re-emergent tremor are very similar to that of rest tremor (Deuschl et al., 1998; Daneault et al., 2013a; Jankovic et al., 1999; Duval, 2006; Duval et al., 2000; Duval et al., 2006; Duval et al., 2005; Henderson et al., 1994). In addition, patients with PD may exhibit action tremor (Louis et al., 2001), a clinical manifestation that we previously observed during slow voluntary movements (Duval et al., 2004). It is important to note that tremor remains the most difficult symptom to treat, as it does not respond well to dopamine replacement therapy compared to other PD symptoms (Koller et al., 1994; Fishman, 2008). To date, surgery remains the most effective treatment for tremor alleviation as lesions in the motor cortex (Bucy, 1945), thalamus (Duval et al., 2000; Duval et al., 2006; Duval et al., 2005; Benabid et al., 1987; Boecker et al., 1997; Fox et al., 1991; Giller and Dewey, 2002; Hurtig and Stern, 1985; Matsumoto et al., 1984; Mosso and Rand, 1975; Narabayashi, 1989; Scott et al., 1970; Tasker et al., 1997), subthalamic nucleus (STN) (Alvarez et al., 2005; Alvarez et al., 2009; Coban et al., 2009; Gill and Heywood, 1997; Merello et al., 2008; Patel et al., 2003; Su and Tseng, 2002; Su et al., 2002; Su et al., 2003; Tseng et al., 2007) or internal globus pallidus (GPi) (Coban et al., 2009; Svennilson et al., 1960; Bronstein et al., 1999; de Bie et al., 2002a; De Bie et al., 2002b; Esselink et al., 2004; Esselink et al., 2006; Hariz and Bergenheim, 2001; Intemann et al., 2001; Samuel et al., 1997; Vitek et al., 2003; Kishore et al., 1997; Laitinen et al., 1992; Lozano et al., 1995) were all shown to reduce or eliminate this symptom of PD. High-frequency stimulation of those same targets (Benabid et al., 1987; Esselink et al., 2004; Esselink et al., 2006; Deiber et al., 1993; Fukuda et al., 2004; Meissner et al., 2005; Ponce and Lozano, 2010) and others (Peppe et al., 2008; Sadikot and Rymar, 2009; Taira, 2012) is also effective in managing PD tremor. Why surgery is efficient in treating tremor will be addressed in more detail later in this paper.

The neural origin of PD tremor (here we are focusing on classical tremor that is present at rest) remains poorly understood. Still, numerous studies have investigated its final common mechanical pathway characteristics, revealing the presence of one main oscillation dominating the spectral signature, usually located between 4 and 6 Hz (Rajput et al., 1991; Deuschl et al., 1998). This tremor is largely independent from external influences, such as loading, indicating that it is centrally generated (Deuschl et al., 1996; Homberg et al., 1987; Meshack and Norman, 2002; Burne et al., 2004). Its amplitude can also fluctuate over time, within seconds or minutes (Beuter and Vasilakos, 1995a; Beuter and Vasilakos, 1995b). Neuronal correlates of PD tremor were also studied in animal models and in humans during surgical procedures. Neural activity related to tremor was observed in numerous brain regions, including the basal ganglia (BG) (Amtage et al., 2009; Amtage et al., 2008; Hurtado et al., 1999; Hutchison et al., 1997; Helmich et al., 2011), thalamus (Helmich et al., 2011; Lenz et al., 1988; Bertrand and Jasper, 1965), cortex (Volkmann et al., 1996; Helmich et al., 2011; Timmermann et al., 2003) and cerebellum (Helmich et al., 2011; Timmermann et al., 2003). Several hypotheses have been put forward to explain how PD tremor is generated and propagated. While attempts were made to involve peripheral or spinal networks (Walker, 1952), there is now a consensus that PD tremor is generated by one or several supraspinal oscillators (Helmich et al., 2012; Brittain et al., 2015; Cagnan et al., 2014). Recently, Helmich et al. (2011) observed brain activity within the cerebello–thalamo––cortical network that co-fluctuated with PD tremor amplitude. They also observed that the onset and offset of PD tremor correlated with GPi activity. This led them to suggest that the BG induces changes in neuronal activity within the cerebello–thalamic network which generates PD tremor. In a subsequent study, Helmich et al. (2012) tested patients presenting with natural fluctuations of tremor amplitude during fMRI. The objective was to assess brain activity during tremor and compare it to periods where tremor was absent. They were able to demonstrate that changes in BG activity preceded the appearance of PD tremor. Changes in PD tremor amplitude was however associated with a change in the cerebello–thalamo–cortical network activity. They concluded that PD tremor is generated by the BG and that it is modulated by the cerebello–thalamo–cortical network. Accordingly, they proposed a "dimmer-switch" model where the BG generates PD tremor and where the latter is modulated in amplitude by the cerebello–thalamo–cortical network. This is an elegant proposition that provides an integrated network involving key brain structures that were identified as playing some role in PD tremor. However, this model, and the experiments that led to its development, did not provide answers about the true source of PD tremor, and a recent study by Cagnan et al. (2014) suggests that this model may be incomplete. Indeed, it is currently not known which structure(s) within the BG, if any, are responsible for generating PD tremor. This is clearly important to attempt the development of improved treatments for this debilitating symptom.

2. An amendment to the "dimmer–switch" model of PD tremor

Below, we will present evidence that will enable us to propose a refined version of the "dimmer–switch" model; the "finger–switch–dimmer-" model; where PD tremor is induced by pathological BG activity (the finger), it is generated by changes in thalamic activity (switch) and modulated by cerebellar activity (dimmer). In order to set the stage for our model, we first present evidence that the thalamus is key to the development of PD tremor. In the experiments presented below, PD tremor was measured using a laser displacement sensor days prior to functional stereotactic neurosurgery, during surgery, and one week postoperatively. The majority of the results from these experiments has previously been published (Duval et al., 2000; Duval et al., 2006; Duval et al., 2005), except for the data related to proprioception, which was presented only in abstract form (Duval et al., 2013). Detailed characteristics of the subjects can be found in (Duval et al., 2005) and each subject signed an informed consent form approved by the institutional research ethics board.