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Research Report

Thalamic physiology of intentional essential tremor is more like cerebellar tremor than postural essential tremor

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ABSTRACT

The neuronal physiological correlates of clinical heterogeneity in human essential tremor are unknown. We now test the hypothesis that thalamic neuronal and EMG activities during intention essential tremor are similar to those of the intention tremor which is characteristic of cerebellar lesions. Thalamic neuronal firing was studied in a cerebellar relay nucleus (ventral intermediate, Vim) and in a pallidal relay nucleus (ventral oral posterior, Vop) during stereotactic surgery for the treatment of tremor. Nine patients with essential tremor were divided clinically into two categories: one with a substantial component of tremor with intention (termed *intention ET*) and the other without (*postural ET*). These types of essential tremor were compared with patients having intention tremor plus other clinical signs of cerebellar disease (*cerebellar tremor*). Neurons in patients with either intention ET or cerebellar tremor had lower firing rates and lower spike × EMG coherence than those in patients with postural ET. Patients with intention ET had a lower spike × EMG phase lead than those with postural ET. Overall, thalamic activity measures of intention ET were different from postural ET but not apparently different from those of cerebellar tremor. One patient with the intention ET (number 4) had a good response to a left thalamotomy and then suffered a right cerebellar hemispheric infarct five years later. After the stroke the intention ET recurred, which is consistent with our hypothesis that intention ET is similar to that of the intention tremor which is characteristic of cerebellar lesions.

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1. Introduction

Essential tremor is one of the most common adult movement disorders (Brin and Koller, 1998; Louis et al., 1998), and can be characterized as tremor which is related to movements or postures of the limbs (Deuschl et al., 1998; Elble, 2006; Elble and Koller, 1990). Recent studies have demonstrated substantial phenotypic variability in essential tremor, which may be a postural tremor or may include a substantial component of intention tremor (Deuschl et al., 2000; Elble and Deuschl, 2011). This intentional component is poorly understood and has not been consistently associated with the measures of pathology, imaging, or central nervous system electrophysiology (Elble and Deuschl, 2011). Human and animal studies suggest that the cerebellum plus related structures, and the thalamus, and the cortex are all involved in the mechanism of essential tremor.

Essential tremor is reduced by surgical lesions or stimulation of a cerebellar and a pallidal receiving nucleus of the thalamus, which are termed ventral intermediate – Vim and ventral oral posterior – Vop, respectively (Fig. 1A)(Hirai and Jones, 1989; Jankovic et al., 1995; Krack et al., 2002; Schuurman et al., 2000). Imaging studies show increased metabolic activation of the cerebellum, thalamus and sensorimotor cortex during essential tremor (Boecker and Brooks, 1998; Jenkins et al., 1993; Perlmutter et al., 2002). Deficits of cerebellar function in patients with essential tremor also suggest that cerebellar inputs to the thalamus and cortex are involved in the mechanism of essential tremor (Deuschl et al., 2000; Helmchen et al., 2003; Stolze et al., 2001).

Intention tremor is defined as tremor which increases in amplitude as the target is approached during visually guided movements. Intention tremor is seen in human subjects with cerebellar pathology or injury to cerebellar pathways, and in monkeys with transient disruption of the deep cerebellar nuclei by cooling through an implanted probe (Flament and Hore, 1988; Vilis and Hore, 1980). These tremors have been termed cerebellar tremor, and it has been proposed that cerebellar injury leads to changes in the timing of outputs from the cerebellum (Lenz et al., 2002; Vilis and Hore, 1980). Similar changes have been found in thalamic neuronal activity, which is consistent with the thalamus being a relay for cerebellar connections to cortex (Lenz et al., 2002).

In some patients, essential tremor has a substantial intentional component in the absence of cerebellar pathology. In other patients, tremor with intention is absent but there is a postural component, with or without a kinetic component. We arbitrarily term these two categories as *intention ET* and *postural ET* (cf Deuschl et al. (1998); Elble and Deuschl (2011); Marsden et al. (1983)). One hypothesis is that essential tremor results from the increased activity of an olivary pacemaker, which transmits tremor related signals to the cerebellum and from there to the thalamus, cortex and periphery (Lamarre, 1995; Llinas, 1984). This is consistent with the finding that neurons in Vim and Vop of these patients show increased firing rates and tremor-related activity that are enabled by active movement (Hua and Lenz, 2005).

We now propose to test an alternate hypothesis that thalamic neuronal and EMG activities during intention ET are similar to those of the intention tremor which is characteristic of cerebellar lesions (cerebellar tremor). In this model, injury to the cerebellum or related structures leads to deafferentation of thalamic nuclei (monkey ventral lateral posterior and human Vim (Hirai and Jones, 1989)), and their cortical targets (Flament and Hore, 1988; Vilis and Hore, 1980). The cerebellar input to these nuclei is excitatory so that deafferentation results in decreased firing rates, and a phase lag in the thalamic spike train × EMG spectrum (Lenz et al., 2002; Vilis and Hore, 1980). We now test this hypothesis by examining thalamic neuronal activity in Vim and Vop during stereotactic thalamotomy in patients with postural ET, intention ET, and with intention tremor plus other signs of cerebellar disease (cerebellar tremor). As a critical test of these two possibilities, we examined the result of a cerebellar lesion in a patient with intention ET that would be predicted to increase tremor due to cerebellar disruption but decrease tremor due to a pacemaker in the cerebellum and related structures.

2. Results

In total, 192 neurons along 57 trajectories were recorded in 13 patients undergoing thalamotomy or thalamic deep brain stimulation for the treatment of tremor. Five patients (54 neurons) with essential tremor were classified as having a substantial intentional component to their tremor, termed *intention ET*. Four essential tremor patients (40 neurons) were found to have an absent intention component, termed *postural ET*. Four patients (112 neurons) had intention tremor and signs of cerebellar disease and were classified as *cerebellar tremor*.

Most patients with essential tremor had a family history or an effect of alcohol upon their tremor or both, which is consistent with a diagnosis of essential tremor (Koller and Busenbark, 1997). The variability in the present population of patients with essential tremor is consistent with the known phenotypical variability of essential tremor including: the nature of the tremor itself (postural and intention ET), the presence of dystonic features and imbalance, plus the association with Parkinson's disease (Elble and Deuschl, 2011). In this setting, other movement disorders occurring with essential tremor, such as non-tremulous cervical dystonia, may be viewed as co-morbidities of essential tremor (Hedera et al., 2010; Schiebler et al., 2011), which do not necessarily effect the ongoing essential tremor.

The control group consisted of recordings from three patients (61 neurons) who underwent surgery for chronic pain in the lower extremities. Some of the present results have been previously reported in separate studies of subjects with essential tremor, or cerebellar tremor, or chronic pain (Hua and Lenz, 2005; Lenz et al., 2002).

2.1. *Thalamic signal*

2.1.1. *Firing rates*

The mean spontaneous firing overall varied significantly with the type of tremor (1-way ANOVA, $F(3,247)=3.75$, $P=0.01$). The mean rate was highest in the postural ET group