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Beta oscillatory neurons in the motor thalamus of movement disorder and pain patients☆

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ABSTRACT

Excessive beta oscillations (15–25 Hz) in the basal ganglia have been linked to the akineto-rigid symptoms of Parkinson's disease (PD) although it remains unclear whether the underlying mechanism is causative or associative. While a number of studies have reported beta activity in the subthalamic nucleus and globus pallidus internus, relatively little is known about the beta rhythm of the motor thalamus and its relation to movement disorders. To test whether thalamic beta oscillations are related to parkinsonian symptoms, we examined the spectral properties of neuronal activity in the ventral thalamic nuclei of five Parkinson's disease patients (two female, age range 50–72 years) and compared them to five essential tremor (three female, aged 41–75) and four central pain patients (one female, aged 38–60). Spike and local field potential recordings were obtained during microelectrode-guided localization of thalamic nuclei prior to the implantation of deep brain stimulating electrodes. A total of 118 movement-related neurons in the region of the ventral intermediate nucleus (Vim) were analyzed across all patient groups. Eighty of these neurons (68%) displayed significant oscillatory firing in the beta range with the limbs at rest. In contrast, only 5.7% of the ventral oral posterior (Vop) (χ^2 test, $p < 0.05$) and only 7.2% of the ventral caudal (Vc) neurons fired rhythmically at beta frequency (χ^2 test, $p < 0.05$). Beta power was significantly decreased during limb movements (ANOVA, $p < 0.05$) and was inversely related to tremor-frequency power during tremor epochs in ET and PD ($r^2 = 0.44$). Comparison between patient groups showed that Vim beta power was significantly higher in ET patients versus pain and PD groups (ANOVA, $p < 0.05$). The findings suggest that beta oscillations are found predominantly in Vim and are involved in movement but are not enhanced in tremor-dominant Parkinson's patients.

Introduction

Parkinson's disease (PD) and essential tremor (ET) are two of the most common tremor disorders. By classical definition (Deuschl et al., 1998; Gelb et al., 1999), parkinsonian tremor is manifested at rest but resolves upon the initiation of a dynamic movement (rest tremor) while tremor in ET is present during kinetic, postural or isometric motor activity but subsides at rest (action tremor). However, it is not uncommon for PD patients to exhibit action tremor (Zimmermann et al., 1994) and for ET patients to exhibit rest tremor (Cohen et al., 2003). PD symptoms arise after the degeneration of dopaminergic neurons of the substantia nigra (Jellinger, 1991) and they include rigidity, bradykinesia or akinesia — antikinetic symptoms that do not occur in pure ET (Gelb et al., 1999). While there is considerable debate regarding the precise histopathological changes in ET (Deuschl and Elble, 2009; Louis et al., 2007; Symanski et al., 2014), it is evident that some form of cerebellar dysfunction is involved in the disorder (Helmchen et al., 2003; Kronenbuerger et al., 2007; Trillenberg et al., 2006). Recent studies have expanded the concept of ET to include gait ataxia by demonstrating that a significant population of ET patients also exhibit cerebellar-like deficits in tandem gait (Fasano et al., 2010; Louis et al., 2010; Stolze et al., 2001). Cerebellar dysfunction may be involved in action and rest tremor as deep brain stimulation (DBS) of the cerebellar zone of the thalamus is consistently effective against both types of tremor (Flora et al., 2010; Narabayashi et al., 1987). The cerebellar area of the thalamus, the ventral intermediate nucleus (Vim),

Abbreviations: BG, basal ganglia; ET, essential tremor; GPi, globus pallidus internus; PD, Parkinson's disease; STN, subthalamic nucleus; Vc, ventral caudal nucleus; Vim, ventral intermediate nucleus; Vop, ventral oral posterior nucleus.

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receives input primarily from the dentate nucleus and projects to the M1 area of the cortex (Na et al., 1997). Anterior to the Vim, the ventral oral posterior (Vop) nucleus receives GABAergic pallidal input and projects to the supplementary motor area (SMA) of the cortex (Inase and Tanji, 1995; Kuo and Carpenter, 1973). While the basal ganglia and cerebellar pathways were previously thought of as segregated and parallel motor loops, a recent finding has demonstrated the presence of a substantial disynaptic connection between the dentate nucleus (output of the cerebellum) and the putamen (input of the basal ganglia) (Hoshi et al., 2005). Some authors have proposed this subcortical connection as a crucial conduit for the propagation of pathological tremorogenic signals between the basal ganglia and the cerebellum (Lewis et al., 2013).

The emergence of normal and abnormal oscillations, primarily beta (13–30 Hz) and tremor (3–8 Hz) frequencies has been observed in a number of motor structures in PD, including the motor cortex, basal ganglia (BG), thalamus and cerebellum (Aumann and Fetz, 2004; Conway et al., 1995; Kuhn et al., 2009; Pfurtscheller et al., 2003; Van Der Werf et al., 2006). Although their precise function remains elusive, beta oscillations are associated with the maintenance of the current motor set at the expense of dynamic, new movement (Engel and Fries, 2010; Jasper and Penfield, 1949). In healthy subjects, beta is suppressed during movement execution but is high during rest and postural maintenance (Kilner et al., 1999; Klostermann et al., 2007). Considering this association of the beta rhythm with tonic motor activity, some groups have suggested that antikinetic parkinsonian symptoms are supported by an aberrant increase of beta power in motor structures (Brown, 2006; Little et al., 2012). Indeed, the increased spatial extent of beta activity in the subthalamic nucleus (STN) correlates with the severity of antikinetic symptoms (Alavi et al., 2013; Pogosyan et al., 2010) and the improvement of these symptoms following dopaminergic treatment correlates with the degree of beta activity suppression (Brown, 2003; Brown et al., 2001; Ray et al., 2008). Beta activity in the STN is also suppressed with DBS, in parallel with improvement in motor performance in PD patients (Kuhn et al., 2008; Wingeier et al., 2006).

The pathology of PD and ET is additionally associated with the occurrence of tremor frequency oscillations (5–8 Hz) across major motor structures (Raethjen and Deuschl, 2012). So-called tremor cells, neurons which discharge coherently with peripheral tremor, have been observed in the motor thalamus, GPi and the STN of PD patients (Chen et al., 2009; Guo et al., 2013; Hua and Lenz, 2005; Lenz et al., 1988b; Levy et al., 2002a, 2002b; Weinberger et al., 2009). However, the relationship between tremor, beta oscillations and dopaminergic degeneration remains unclear. The dependence of rest tremor severity on nigrostriatal dopamine depletion is comparatively weak (Benamer et al., 2000; Helmich et al., 2012; Pirker, 2003) and dopaminergic therapy is less efficacious against rest tremor than against bradykinesia and rigidity (Fishman, 2008; Koller et al., 1994). Increased beta oscillations, while strongly associated with akineto-rigid symptoms, do not exacerbate tremor (Zaidel et al., 2009). On the contrary, an increase in cortical beta power coincides with tremor suppression following benzodiazepine intake (Ibanez et al., 2014). It is also unknown how beta band activity in the motor thalamus (Holdefer et al., 2010; Paradiso et al., 2004) contributes to the manifestation of akineto-rigid symptoms. Deep brain stimulation (DBS) or ablation of Vim consistently improves tremor symptoms but does not improve akinesia, bradykinesia or rigidity (Benabid et al., 1996; Lenz et al., 1994; Lozano, 2000). To further elucidate the role of the Vim beta rhythm in PD, we examined spike oscillatory activity in the ventral thalamus of PD, ET and central pain patients. We hypothesized that the incidence of beta-oscillatory cells and beta power would be higher in the Vim of parkinsonian patients than in the Vim of patients with no known dopaminergic deficiency (ET and pain patients). During tremor epochs, we expected beta power to diminish with a concomitant increase in tremor band power.

Material and methods

Patients

Microelectrode recordings were obtained from 14 patients (6 female)undergoing implantation of deep brain stimulating electrodes for the treatment of movement disorders or pain. The group consisted of patients with PD ($n = 5$, mean age $\pm$ st.dev 65.6 $\pm$ 9.0 years), ET ($n = 5$, 50 $\pm$ 11.2 years) and pain ($n = 4$, 56.6 $\pm$ 13.7). Pre-operative clinical assessment of all the patients was performed by a neurologist at Toronto Western Hospital using the Unified Parkinson's Disease Rating Scale (UPDRS), the Fahn–Tolosa–Marin tremor scale (Fahn, 1987) and the Toronto Western Hospital Pain Assessment. During recording, all ET patients presented with action tremor (induced by maintenance of tremorogenic posture) and all but one PD patient had resting tremor. The third group consisted of patients with chronic pain resulting from multiple sclerosis ($n = 2$) and stroke ($n = 2$) but no movement disorder such as tremor, rigidity or bradykinesia. Clinical and demographic details of the patients are given in Table 1. Recordings were made in each patient while awake with local anesthesia and PD patients were withdrawn from all medications 12 h prior to surgery. The protocol used in these studies was reviewed and approved by the University Health Network Ethical Review Board, University of Toronto. All patients gave free and informed consent to participate in the study.

Recordings

Detailed descriptions of the intraoperative techniques used in this study have been previously published (Lenz et al., 1988a; Tasker et al., 1998). Physiologic exploration of the thalamus was carried out with dual microelectrodes after determination of stereotactic targets with MR imaging procedures for the placement of DBS electrodes. The stereotactic coordinates of the anterior commissure (AC) and posterior commissure (PC) were determined by 1.5 T magnetic resonance imaging and were used to estimate the location of the ventral thalamic nuclear group based on the 14.5 mm sagittal section of the standard atlas of Schaltenbrand and Wahren (1977). For Vim procedures, the anterior–posterior coordinate (Y) was at the midcommissural point and the superior–inferior coordinate (Z) was on the AC–PC line. The sagittal map was reformatted by computer to conform to the patient's own AC–PC length. Physiologic discrimination of the ventral thalamic nuclei was performed using single-unit and LFP recordings (10–30 Hz bandpass) obtained from two microelectrodes (about 25 μm tip length, axes 600 μm apart, about 0.2-MΩ impedance at 1000 Hz) that traversed the thalamus in an anterodorsal to ventroposterior direction. First, individual cells along the trajectory were tested for responses to movement. With the patient otherwise at rest, the limb was moved about the wrist, elbow or shoulder (passive movement) by the neurosurgeon and the neuronal response was recorded concomitantly with the accelerometer signal. Patients were also asked to perform voluntary movements about the wrist, elbow or shoulder and the neuronal responses were recorded (active movements). Cells that were responsive to passive or active movements were considered movement-related cells of the motor thalamus (Vop/Vim) (Molnar et al., 2005). Additionally, microstimulation (100 μA, 200 Hz, 1 s, pulse width 0.3 s) was conducted every 1 mm along the trajectory of the microelectrode. The first site in the track where microstimulation-induced paresthesia was observed was considered to be the anterior border of Vc. This reference point was used to reconstruct the location of neurons to specific thalamic subnuclei (Vop and Vim) using the specific angle of the trajectory and the atlas template map, customized to each patient as described above (Fig. 1a).

For Vim cells, recordings were collected during the three conditions 1.) Baseline — with the limbs at rest, 2.) Movement — during active or passive movements of the contralateral limb and 3.) Tremor — during rest (PD) or action tremor (ET). While tremor occurred spontaneously