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Neuronal activity patterns in the ventral thalamus: Comparison between Parkinson's disease and cervical dystonia

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HIGHLIGHTS

- The ventral thalamus was characterised by five common patterns in both PD and CD.
- There were no specific patterns or differences in distribution between PD and CD.
- Burst patterns and characteristics had an unbalanced distribution between PD and CD.

ABSTRACT

Objective: The aim of this study was to distinguish neuronal activity patterns in the human ventral thalamus and reveal common and disease-specific features in patients with Parkinson's disease (PD) and cervical dystonia (CD).
Methods: Single unit activity of neurons was recorded during microelectrode-guided thalamotomies. We classified neurons of surgical target and surrounding area into patterns and compared their characteristics and responsiveness to voluntary movement between PD and CD patients.
Results: We distinguished five patterns of neuronal activity: single, LTS burst, mixed, non-LTS burst and longburst patterns. The burst and mixed patterns showed significant differences in several basic and burst characteristics. We showed that there were no disease-specific patterns or significant differences in pattern distribution between studied patients. However, burst patterns had an unbalanced distribution between disease conditions. In addition, we found difference in LTS burst characteristics between surgical targets and surrounding nuclei. All identified patterns, except the long burst pattern, were reactive to the motor tasks and to contraction of the pathological muscles.
Conclusions: The ventral thalamus was characterised by common neuronal activity patterns which differed in characteristics between PD and CD.
Significance: Our findings highlight patterns of neuronal activity of the human ventral thalamus and specific pathological features.

1. Introduction

The thalamus plays a crucial role in many brain functions, serving as an information gate for afferent sensory signals, efferent programmes and intercortical interactions. Along with a complex inner structure, the thalamus has widespread connections with subcortical structures (basal ganglia, cerebellum, midbrain and others), different cortical regions and the peripheral nervous system (Jones, 2007; Sherman and Guillery, 2013). Thus, such extensive connectivity implies a complexity and diversity of neuronal activity patterns.

It has previously been demonstrated that the thalamus could be characterised by at least two different modes of neuronal activity:

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burst and tonic mode (Llinás and Jahnsen, 1982; McCormick and Bal, 1997). The burst activity of thalamic neurons is attributed to the intrinsic properties of these cells. Membrane hyperpolarisation deactivates a low-threshold calcium channel and the subsequent depolarisation leads to a low-threshold calcium spike (LTS) followed by a burst of sodium-generated action potentials (Steriade, 1997, 2000). Animal studies showed that a bursting oscillatory pattern depresses the response to afferent inputs and it has been observed during sleep or under anaesthesia. Tonic or relay mode has high sensitivity to afferent inputs and has been observed during wakefulness (Llinás and Steriade, 2006; Steriade, 1997, 2000). Thereby, it was thought that only tonic firing may exist in the awake state (McCormick and Bal, 1997).

Nevertheless, other studies showed that bursting activity may occur in healthy behaving animals in awake state (Ramcharan et al., 2000). Authors found that the extent of bursting was greater in the higher-order than in the first-order thalamic nuclei and this increased bursting correlated with lower spontaneous activity in the higher-order relays (Ramcharan et al., 2000, 2005). If bursting effectively signals the introduction of new information to a cortical area, as suggested, this increased bursting may be more important in corticocortical transmission than in transmission of primary information to the cortex (Ramcharan et al., 2005).

The possibility that bursting patterns may exist in a awake state also fits with results obtained in patients undergoing functional stereotactic neurosurgery (Jeanmonod et al., 1996; Lenz et al., 1989, 1994; Ohara et al., 2007; Rinaldi et al., 1991). Indeed, bursting activity was observed in medial and lateral thalamic nuclei of awake chronic pain patients suggesting that this activity may be related to the patient's pain (Rinaldi et al., 1991). However, similar bursting activity was found in non-pain patients, reflecting that there may not be a simple association between bursting activity and pain (Ohye et al., 1972; Radhakrishnan et al., 1999).

There is also some controversy over the bursting cell responsiveness. Some studies reported an arreactivity of LTS bursts and therefore consider them to be associated with the pathology (Magnin et al., 2000). Nevertheless, it has been shown that thalamic LTS burst firing rate altered from baseline during sensory stimuli, motor events (Lee et al., 2005) and mental arithmetic (Kim et al., 2009). Analysis of evoked activity patterns of human ventrolateral thalamic neurons revealed that realisation of verbally-ordered voluntary movement caused responses of both tonic and burst type in neurons of patients with Parkinson's disease (Raeva et al., 1999a). Moreover, the appearance of short-term local synchronisation of the activity between tonic and burst thalamic cells was observed during or immediately following movement performance in patients with Parkinson's disease (Raeva et al., 1999a) and cervical dystonia (Sedov et al., 2014).

Exploration of ventral thalamic nuclei is of particular interest due to their involvement in movement organisations and is one of the major targets for surgical treatment of movement disorders (Hamani et al., 2006). The purpose of this paper is to provide a comparison of physiological properties of ventral thalamic neurons of Parkinson's disease (PD) and cervical dystonia (CD). There is a well-established model of basal ganglia which applies to PD (Alexander et al., 1986), according to which the thalamus is hyperpolarised which results in the predominance of burst activity. At the same time, the mechanisms of CD remain murky. We predict that if the bursting is a reflection of the pathology, the surgical target area (Voi, Vim) will contain more bursting activity than the surrounding area (Voa, Vop). On the other hand, surgical targets are nuclei receiving input from the deep cerebellar nuclei, while in the surrounding area the nuclei receive input from the pallidum. In this case, we predict more bursting patterns in surrounding nuclei.

2. Methods

2.1. Patient population

We analysed the spontaneous single unit activity and motor responses of ventral thalamic neurons recorded from 10 CD (4 males, 6 females, age 38.4 ± 5.0) and 14 PD (8 males, 6 females, age 54.4 ± 7.7) patients (Supplementary Table S1). These recordings were part of the microelectrode-guided thalamic mapping which preceded surgical ablation procedures. Surgeries were carried out at the N.N. Burdenko Neurosurgery Institute and at the Research Centre of Neurology. All PD patients had the diagnosis of idiopathic PD based on medical history, physical and neurological examinations, response to levodopa ordopaminergic drugs, laboratory tests, and MRI or CT scans to exclude other diseases. All PD patients had at least a mild tremor. They were assessed with Hoehn and Yahr staging while off their medications. All CD patients had the diagnosis of idiopathic CD based on medical history, physical and neurological examinations. All CD patients hadbotulinum toxin treatment. CD patients had torticollis or combined tortico-laterocollis. Most of them had also jerky head tremor.

The surgical procedure was carefully explained to the patients before the operation. All participants gave written informed consent. The study protocol was approved by the local Ethics Committees, in agreement with the Declaration of Helsinki.

2.2. Surgical procedures and data collection

The selected surgical targets for ablation were the ventral oral internal nucleus (Voi) for CD (Bertrand et al., 1978; Mundinger and Riechert, 1961) and the ventral intermediate nucleus (Vim) for PD (Tasker et al., 1988). Preoperatively, all patients underwent MRI or CT scanning with the stereotactic frame positioned. The surgical target location was confirmed with the Shaltenbrand-Wahren brain atlas (Schaltenbrand and Wahren, 1998). Intraoperatively, electrophysiologic guidance with microelectrode recordings (MER), functional testing and macro-stimulation of an awake patient were used to verify the correct target location. The electrode was inserted 15–25 mm above the target site and was advanced 0.1–0.5 mm along its trajectory so we could register not only the neuronal activity immediately in the surgical target region but also in the surrounding ventral thalamic nuclei (Voa-Vop).

The procedure was performed under local anaesthesia. The recording protocol included periods of spontaneous activity at rest and during the execution of voluntary movements. In the current study, we choose two types of motor tests: (1) elevation of a shoulder and (2) clenching a fist. Thus, we examined neuronal reactions associated with neck muscles involved in CD pathology and wrist muscles affected by PD. Thereby we could explore neuronal reactions to contraction of muscles whether or not they are directly involved in the pathology for each disease. The pathological neuronal activity during the periodic occurrences of spontaneous dystonic contractions of neck muscles in patients with CD and during the tremor episodes in patients with PD was indicated based on the corresponding electromyography (EMG) changes.

Extracellular single unit activity of neurons was recorded using tungsten microelectrodes with a tip diameter of 1–2 mkm (resistance 0.5–1 MΩ). EMG of finger (flexor and extensor) and neck (sternocleidomastoideus, trapezius, splenius) muscles and an audio channel of the instructions to the patient were also recorded simultaneously.