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RESEARCH ARTICLE

Spontaneous low threshold spike bursting in awake humans is different in different lateral thalamic nuclei

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Abstract Spontaneous action potential bursts associated with low threshold calcium spikes (LTS) occur in multiple human lateral thalamic nuclei, each with different physiologic characteristics. We now test the hypothesis that different patterns of spontaneous LTS bursting occur in these nuclei during awake surgery in patients with essential tremor and the arm at rest. This protocol was chosen to minimize the effect of the patient's disease upon thalamic activity which is a potential confound in a surgical study of this type. Neuronal activity was studied in the human thalamic nuclei receiving somatic sensory input (Vc, ventral caudal), input from the deep cerebellar nuclei (Vim, ventral intermediate), or input from the pallidum (Vo, ventral oral). In each nucleus the burst rates were significantly greater than zero. Burst rates were higher in Vc than in Vim, while firing rates were lower. These findings suggest that neurons in Vc are hyperpolarized and have more frequent inhibitory events. Pre-burst inter-spike intervals (ISIs) were significantly longer in Vc, but were significantly shorter when corrected for the average ISIs between bursts (burst rate/inverse of the primary event rate). These results suggest that inhibitory events in Vc are of lower magnitude relative to a hyperpolarized resting membrane potential. Studies in many species demonstrate that input from the pallidum to the thalamus is inhibitory, suggesting that input to Vo is predominantly inhibitory. However, neurons in Vo have neither slower firing rates nor more frequent LTS bursts. Previous studies have found that spontaneous LTS is similar between classes of neurons within Vc, as defined by their response to thermal and painful stimuli. The differences in spontaneous LTS between human nuclei but not between functional classes within a nucleus may be a basic organizing principle of thalamic inhibitory circuitry.

Keywords Human thalamus · Principal somatic sensory nucleus · Ventral lateral nucleus · Low threshold spike · Action potential burst · IPSP · Essential tremor

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Introduction

Bursts of action potentials have previously been reported in the multiple nuclei of the human thalamus (Lenz et al. 1989; Jeanmonod et al. 1996; Zirh et al. 1997; Radhakrishnan et al. 1999). These bursts are defined by pre-burst inhibition or silent periods and by short inter-spike intervals within bursts (ISIs) which become longer throughout the burst. These burst characteristics are consistent with bursts associated with low threshold calcium spikes (LTS) based on intracellular recordings in old world monkeys and non-primate species (Steriade et al. 1990; Ramcharan et al. 2000b).

Increased LTS bursting has been reported to occur in the thalamus of patients with some types of chronic pain (Lenz et al. 1994; Radhakrishnan et al. 1999; Jeanmonod et al. 1996), Parkinson's tremor, dystonia, Parkinson's disease, tinnitus, and psychiatric disease (Zirh et al. 1997; Jeanmonod et al. 1996). These neuronal spike trains have been recorded in medial or intralaminar

nuclei, in Vc, in a cerebellar INPUT receiving nucleus (Vim, ventral intermediate), and a pallidal INPUT receiving nucleus (Vo, ventral oral). Each of these studies examined LTS bursting in a different thalamic nuclei specific to the diagnosis.

Different thalamic nuclei have different anatomic and physiologic characteristics. For example, Vim and Vc receive excitatory input from the deep cerebellar nuclei and the dorsal column nuclei/spinal cord, respectively (Apkarian and Hodge 1989; Steriade et al. 1997; Sherman and Guillery 2001). Studies in non-human species demonstrate that the pallidum sends an inhibitory projection to pallidal INPUT receiving nucleus which suggests that human Vo receives inhibitory input from the pallidum (DeLong 1990; Steriade et al. 1997; Sherman and Guillery 2001). The effect of the differences between nuclei upon LTS bursting is lost in prior human studies since different nuclei were studied in each diagnosis. Therefore, we now test the hypothesis that different patterns of spontaneous LTS bursting occur in different lateral thalamic nuclei in patients with essential tremor (ET) with the arm at rest (see Discussion).

We studied subjects with ET because it is a mono-symptomatic illness, without the complex clinical pattern (Deuschl et al. 1998; Elble 2002) and anatomic/physiologic abnormalities of PD and other neurologic diseases treated with thalamic surgery (Elble and Koller 1990; Deuschl et al. 1996). We studied thalamic activity with the arm at rest because of the absence of tremor dependent activity in that state (Hua and Lenz 2005). The results of this study identify significant, complex, differences in spontaneous LTS bursting between different thalamic nuclei in awake humans.

Materials and methods

These studies were carried out at the Johns Hopkins Hospital (1993–2005) during the physiologic exploration of the thalamus which preceded implantation of deep brain stimulation (DBS) electrodes in Vim or Vim thalamotomy for treatment of ET (Koller et al. 2001). The diagnosis was confirmed in each case by a neurologist specializing in movement disorders. Exclusions were patients with other diagnoses in addition to ET, such as Parkinson's tremor, torticollis, and cerebellar syndromes (Jankovic 2002). The protocol was reviewed and approved annually by the Institutional Review Board of the Johns Hopkins University. All patients signed an informed consent for these studies. All methods used here have been previously described (Lee et al. 2005).

Intraoperative procedures

Thalamic exploration was performed as a stereotactic procedure using the Leksell frame with patients off tremor medications for 18 h. First, the frame coordinates of the anterior (AC) and posterior (PC) commissures were measured by magnetic resonance imaging or computed tomography. These coordinates were used to estimate the nuclear locations. Physiological corroboration of nuclear location was then performed under local anesthesia without sedation (i.e., subject fully conscious) by single unit recording and microstimulation through a microelectrode. We used a platinum–iridium electrode etched to a tip of 3–4 μm and coated with solder glass to give an impedance of approximately 2.5 MΩ, which was reduced to approximately 0.5 MΩ by microstimulation (50 μA) in the brain. The electrode was advanced toward the Vc as localized by pre-operative imaging. Microstimulation was delivered in trains of 1s duration at 300 Hz by using a biphasic pulse consisting of a 0.2-ms anodal pulse followed in 0.1 ms by a cathodal pulse of the same duration and magnitude. Stimulation was initially carried out at 40 or 50 μA at sites located 2 mm apart along the trajectory. When a response was evoked, then a threshold was established.

The signals recorded on magnetic tape (Model 4000, Vetter Corp., Rebersberg, PA, USA) during the procedure included: the foot pedal indicating events during the examination, the microelectrode signal, electromyograms (EMGs), and the audio channel describing instructions to the patient, application of stimuli, etc. Additional digital recording of a foot pedal and of microelectrode signal was made with a Cambridge Electronic Design (CED) 1401 interface at 500 and 50 KHz, respectively.

The initial trajectories were always focused on Vc because the response of neurons in this area to cutaneous and deep mechanical stimulation provides the most reliable estimate of the boundaries of the adjacent thalamic nucleus Vim, (Lenz et al. 1995; Garonzik et al. 2002; Lee et al. 2005).

Study of thalamic activity

When a neuron was isolated, spontaneous activity was first recorded. The activity of the isolated neuron was then studied to identify neurons responding to cutaneous stimuli such as light touch, tapping or pressure to skin (cutaneous sensory neurons), or to deep stimuli such as pressure to muscles or ligaments and passive joint movement (deep sensory neurons). These neurons were also characterized by their receptive field

(RF). The activity of neurons was also examined as patients carried out movements such as making a fist, flexing or extending the wrist and elbow, pointing, etc. We carried out microstimulation along each trajectory, as previously described (Ohara and Lenz 2003).

The anterior and inferior borders of Vc were identified by the most anterior and inferior deep or cutaneous neuron in the region where the majority of neurons responded to either deep or cutaneous stimuli (Lee et al. 2005). These points and the location of the AC PC line were used to overlay the map of the recording data with a sagittal thalamic atlas map (Schaltenbrand and Bailey 1959). The nuclear location of any recorded neuron was inferred from this overlay.

Data analysis

Post-operatively, the spike train was digitized at 20 kHz and stored on a PC, together with the foot pedal signals at 200 Hz. Digitally recorded spike train signals were analyzed using Spike2 software (CED, Cambridge, UK) that allowed for template-matching of waveforms. Subsequent analyses of spike characteristics (e.g., firing rate, ISI) including burst detection were carried out using MATLAB (Mathworks, Natick, MA). Analysis of bursting was carried out on spontaneous activity with eyes open and with the arm at rest. The absence of tremor was confirmed by visual inspection of both the limbs and the EMG signal.

Analysis of burst activity

Low threshold calcium spike bursts were identified by the criteria used in the studies of awake monkeys which were based on intracellular confirmation in a cynomologous monkey thalamic slice (Ramcharan et al. 2000a, b). The criteria (50-6-16) to select these bursts were as follows: the inter-spike interval (ISI) preceding the first action potential in the burst had a duration of >50 ms, the ISI following the first action potential in the burst had a duration of <6 ms, and all following action potentials are considered as part of the burst if their ISI was less than 2 ms longer than the preceding ISI, up to maximum ISI of 16 ms. We have repeatedly illustrated the use of these techniques and burst criteria (for example, Lee et al. 2005; Lenz et al. 1998).

A pre-burst inhibition of 100 ms is required to produce a maximal LTS burst (Jahnsen and Llinas 1984a). Therefore, the 50 ms pre-burst ISI criterion may select submaximal LTS bursts or non-LTS bursts. Therefore, we examined the null hypothesis that the bursts identified by these criteria were not maximal LTS bursts. This hypothesis was rejected when the confidence interval of the mean pre-burst ISI was significantly less than 100 ms.

We also measured the primary event rate which includes all spikes not in bursts plus the first spike in each burst and so is a measure of the rate of spikes occurring between bursts (McCarley et al. 1983; Cox and Lewis 1966). As an indicator of the relationship between bursting and average neuronal depolarization, we calculated burst rate/primary event rate. If the difference in burst rates between two neuron types is lost when this ratio is calculated, then the difference in bursting is relatively dependent on the primary event rate. All firing indexes including bursts were compared by nuclear locations in the thalamus.

Statistical analysis

All spike train and burst indices were compared between thalamic nuclei (Vo, Vim and Vc) using one-way ANOVAs by nucleus. Post hoc analysis was carried out by Tukey's honestly significant difference (HSD). The confidence interval (CI) for a given index of neuronal firing by nucleus was determined based on Bonferroni corrected experiment-wise estimate of error. Specifically, we estimated the 95% CI by the mean $\pm$ 2.39 SEM which was indicated by the lower and upper limits of this interval, i.e. (CI lower–upper). The null hypothesis was rejected at $P < 0.05$ for all tests.

Results

These results were carried out in 19 patients with ET undergoing implantation of Vim-DBS ($N = 5$) or Vim-thalamotomy ($N = 14$). These patients included ten men (50 to 79 years old) and nine women (41 to 87 years old). Surgery was carried out on the right thalamus in 3 patients, and on the left in 16 patients. For each patient, one to six trajectories were explored (mean 3.3). A total of 142 neurons were studied with nuclear locations as follows: Vo 21, Vim 97, and Vc 24.

Firing rates

As suggested by Fig. 1, firing rates of neurons were significantly different between neurons in different nuclei ($F = 7.0$, $df = 2$, $P = 0.001$, one-way ANOVA, Fig. 2a). Post hoc testing (Tukey's HSD) demonstrated that firing rates in Vc were significantly lower than those in Vo ($P < 0.001$) (Fig. 2). Theoretical studies suggest that the neuronal firing patterns will not respond to inhibitory inputs unless the baseline firing rate is greater than

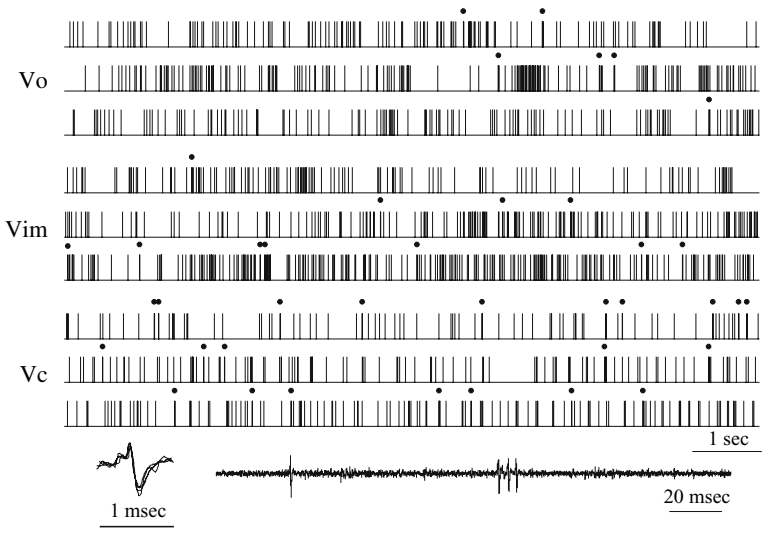

Fig. 1 Spontaneous (eyes open) spike trains of a single neuron in *Vo*, *Vim*, and *Vc*. Each *vertical tic* indicates the occurrence of an action potential and each *dot* above the spike train indicates the occurrence of a burst, as identified by the criteria given in the Methods section: 'Analysis of Burst Activity'. The lowest trace shows the raw Vc spike train which includes the burst between 4 and 5 s; shapes of the discriminated spikes are shown to the *left*. The calibrations are as indicated

50 Hz (Smith and Sherman 2002). For neurons in Vo the average firing rates were significantly less than 50 Hz (CI 8.5–33.2 s^{-1}), suggesting that inhibitory events do not dominate their activity.

We next examined the primary event rate (see Methods). Primary event rates were significantly different between nuclei ($F = 7.2$, $df = 2$, $P = 0.001$, Fig. 2b). This measure of basal firing rates was significantly lower ($P < 0.001$, Tukey's HSD) in Vc than in Vim. The primary event rates in Vo were significantly less than 50 Hz (CI: 15.2–25.4 s^{-1}). The lower firing rates (firing rate and primary event rate) suggest that neurons in Vc are relatively less depolarized than neurons in the other nuclei.

Bursting rates

Neurons in all three nuclei had burst rates greater than zero (CI: Vo 0.17–0.39 s^{-1}, Vim 0.36–0.58 s^{-1}, Vc 0.34–0.90 s^{-1}). Burst rates were significantly different between nuclei ($F = 3.2$, $df = 2$, $P = 0.044$, one-way ANOVA, Fig. 3a). Burst rates were significantly higher in Vc than in Vo ($P = 0.031$, Tukey's HSD). This difference in the burst rate might be a result of higher firing rates leading to more frequent individual and grouped short ISIs. In that case burst rates would be dependent upon the basal firing rate, and the ratio of burst rate to primary event rate would not confirm the inter-nuclear differences identified by the burst rate.

The ratio of burst rate/primary event rate was significantly different between nuclei ($F = 12.2$, $df = 2$, $P < 0.001$, one-way ANOVA, Fig. 3b). The ratio was significantly higher in Vc than in either Vim ($P < 0.001$, Tukey's HSD) or Vo ($P = 0.018$). The burst rates and ratios in Vc were higher than in the other nuclei (Fig. 3). Therefore, the higher burst rate in Vc does not depend upon the basal firing rate, which is lower in Vc.

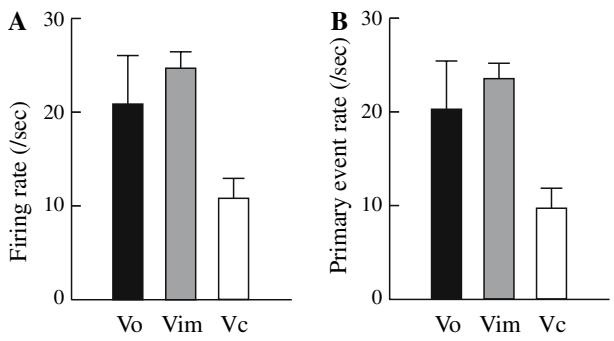

Fig. 2 Firing rates for neurons in thalamic nuclei *Vc*, *Vim*, and *Vo*. **a** The overall firing rate for all action potentials occurring in the spike train. **b** The primary event rate for all action potentials not included in bursts except the first action potential in each burst. The plots are the mean with *error bars* of 2.39 × SEM (Bonferroni corrected experiment-wise error rate). See text

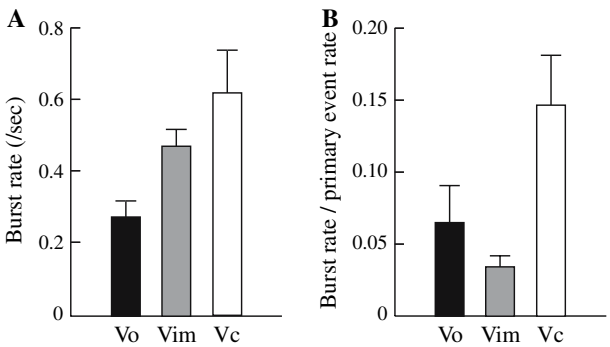

Fig. 3 Burst rates for neurons in thalamic nuclei *Vc*, *Vim* and *Vo*. **a** The burst rate. **b** The burst rate/primary event rate. This ratio corrects for the tendency of spike trains with high firing rates to include groups of action potentials with short ISIs which might be confused with LTS bursts. Other conventions as in Fig. 2

Pre-burst inhibition

The pre-burst ISI or silent period is a defining property of thalamic LTS bursts which we studied in order to characterize thalamic bursts. We examined whether pre-burst ISIs were significantly different from 100 ms because a pre-burst inhibition of 100 ms is required to produce a maximal LTS burst (Steriade et al. 1990). The pre-burst ISIs were significantly longer than 100 ms for all three nuclei (CI: Vo 118–329 ms, Vim 111–213 ms, Vc 174–650 ms). The pre-burst ISI was significantly different between nuclei ($F = 7.9$, $df = 2$, $P < 0.001$, one-way ANOVA, Fig. 4a). Post hoc testing revealed that pre-burst ISIs were significantly longer in Vc than in Vim ($P < 0.001$, Tukey's HSD). These longer ISIs might result from slower firing rates in Vc as shown in Fig. 2. In that case the ratio of the pre-burst ISI to the average ISI between bursts (inverse of primary event rate) would not be significantly different from 1.

We next tested whether this ratio was significantly different between nuclei. The ratio of pre-burst ISI/inverse of primary event rate was significantly greater than 1 for all neurons (CI: Vo 1.2–3.1, Vim 2.3–2.9, Vc 1.2–2.0). Therefore, we conclude that the pre-burst inhibition for all nuclei was consistent with maximal spontaneous LTS bursts.

The magnitude of the ratio of pre-burst ISI/inverse of primary event rate may reflect the magnitude of the pre-burst hyperpolarization (Jahnsen and Llinas 1984a). This ratio was significantly different ($F = 6.4$, $df = 2$, $P = 0.002$, one-way ANOVA, Fig. 4b) between nuclei. The post hoc testing revealed that the ratio of pre-burst ISI/inverse of the primary event rate was significantly smaller in Vc than in Vim ($P = 0.001$, Tukey's HSD), although the pre-burst ISI was longer. Therefore, the longer pre-burst ISIs in Vc (Fig. 4a) are a reflection of the lower basal firing rates in Vc perhaps resulting from a greater level of hyperpolarization.

The number of action potentials in a LTS burst is a function of the size of the underlying LTS (Jahnsen and Llinas 1984a). The average number of action potentials was not significantly different ($F = 1.0$, $df = 2$, $P = 0.377$, one-way ANOVA) between neurons in the different nuclei. Therefore, the significant inter-nuclear differences in the pre-burst ISI and the ratio did not result in significant differences in the number of action potentials per burst (Steriade et al. 1997; Sherman and Guillery 2001).

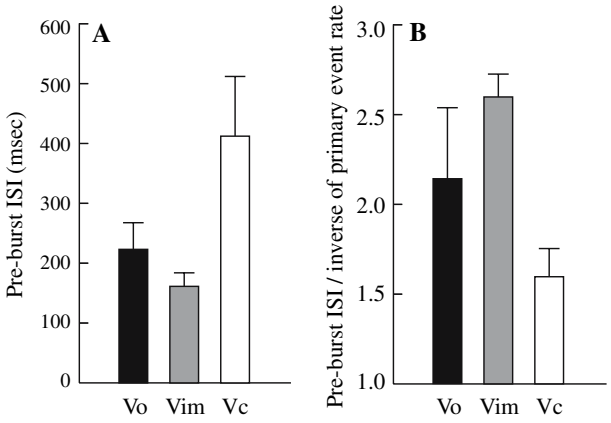

Fig. 4 Indicators of pre-burst inhibitory events. **a** Pre-burst ISI. **b** ratio of pre-burst ISI/inverse of the primary event rate which indicates the extent to which the pre-burst ISI is shorter than non-burst ISIs in the spike train. The ratio is an indicator of the strength of inhibition. Conventions as in Fig. 2

Discussion

The present study demonstrates that spontaneous LTS bursting and significant pre-burst inhibition occur in human thalamic nuclei Vc, Vim and Vo. Neurons in Vc had lower firing rates. The LTS burst rate and burst/primary event rate are higher in Vc while the pre-burst ISI/inverse of primary event rate is smaller in Vc. These results suggest that Vc neurons are more hyperpolarized, while pre-burst inhibitory events are more frequent but of lower magnitude. Although Vo receives inhibitory (pallidal) inputs, it has significantly higher firing rates and lower LTS burst rates. These results demonstrate that the properties of spontaneous LTS bursting in Vc, Vim and Vo of awake humans are characterized by complex inter-nuclear differences.

Methodologic concerns

There are no human intracellular studies of spike burst firing patterns. Therefore we relied on the only primate intracellular studies available which were carried out in cynomologous monkey thalamic slice (Ramcharan et al. 2000a, b). This study employed the 50-06-16 criteria for identifying LTS bursting in primates (see Analysis of Burst Activity in Methods section) (Ramcharan et al. 2000a)

Most human studies have used the 20-6-15 criteria (Lenz et al. 1994; Radhakrishnan et al. 1999; Jeanmonod et al. 1996; Lenz and Dougherty 1998). Other criteria have also been used to identify LTS bursting in primates, such as the 100-4-4 and the present 50-06-16 criteria (Ramcharan et al. 2000a, b). These different criteria may have minimal effect on the results since

frequencies of LTS bursting are not significant between different monkey thalamic neuron types and behavioral states (Ramcharan et al. 2000b).

In the human literature LTS bursting was studied in different nuclei for each diagnosis, complicating the interpretation of the effect of inter-nuclear differences in LTS bursting (Jeanmonod et al. 1996; Lenz et al. 1994). Therefore, we studied patients with an uncomplicated diagnosis of ET. Uncomplicated ET was chosen because of the absence of symptoms other than tremor, and the lack of complex abnormalities of the central nervous system, unlike other diagnoses in patients undergoing thalamic surgery (Deuschl et al. 1998; Elble 2002). Nevertheless, the higher basal firing rates in Vim may be consistent with the increased cerebellar ouflow in ET, although ET dependent activity in Vim is minimal with the arm at rest, as in the present study (Jenkins et al. 1993; Hua et al. 1998; Hua and Lenz 2005; Molnar et al. 2005).

The thalamic firing rates in patients with chronic pain are very similar to those in patients ET, and both patient groups were studied with the arm at rest. Firing rates, but not burst rates, of neurons in Vc, Vim and Vop in patients with chronic pain are indistinguishable from the present rates in the corresponding nuclei of patients with ET with the arm at rest (Lenz et al. 1994, 2002). The firing rates of neurons in Vim and Vop in patients with chronic pain are not significantly different from each other, and are greater than those in Vc of patients with chronic pain (Lenz et al. 2002), as in the present results. All these results strongly suggest that firing rates in Vim of patients with ET are in the normal range when the arm is at rest.

Mechanism of bursting activity

To test whether these bursts are the result of LTS we examined the spike train for evidence of pre-burst inhibition by measuring by the ratio of the pre-burst ISI/inverse of the primary event rate. Neurons in all three nuclei had average ratios significantly greater than 1 which demonstrates significant pre-burst inhibition (Fig. 4). Maximal LTS occurs following a pre-burst inhibition of 100 ms (Jahnsen and Llinas 1984a). In the present study, bursts were selected by criteria which required a pre-burst interval of greater than 50 ms. Nevertheless, neurons in all nuclei had pre-burst silent periods significantly greater than 100 ms. This result demonstrates the presence of pre-burst inhibition consistent with maximal LTS in spontaneous LTS bursts recorded in Vo, Vim and Vc (Jahnsen and Llinas 1984b; Ramcharan et al. 2000a).

Differences in LTS bursting between different thalamic nuclei

Firing rates were lower in Vc than in Vim (Fig. 2) in patients with ET with the arm at rest (Hua and Lenz 2005). In these patients firing rates in Vim are said to be approximately equal to those in Vop, consistent with the present results (Fig. 2) (Molnar et al. 2005). The present firing rates might have been higher in Vim with posture than with the arm at rest (Hua and Lenz 2005). The present results demonstrate that with the arm at rest firing rates are lower in Vc, perhaps as a result of a hyperpolarized membrane potential.

As noted above, neurons in Vc have lower firing rates, and higher LTS burst rates, even after correction for primary event rates (Fig. 2). This is consistent with the finding that higher burst rates were found in monkey ventral posterior lateral nucleus of thalamus, corresponding to human Vc (Hirai and Jones 1989), than in the lateral geniculate (Ramcharan et al. 2000b). These results suggest that Vc is an outlier among thalamic nuclei characterized by lower firing rates, higher LTS burst rates, and lower ratio of pre-burst ISI/inverse of the primary event rate. Therefore, the higher LTS burst rates in Vc may be the result of more frequent, smaller, inhibitory events against a background of hyperpolarization. The rate of bursting may also vary between different thalamic nuclei as a result of inter-nuclear differences in the composition of proteins mediating the properties of LTS conductances, such as thresholds (Perez-Reyes 2003).

The most striking physiologic difference between the nuclei studied in many species is the difference in non-cortical inputs to Vo as compared with Vim and Vc (Steriade et al. 1997). Based upon studies in a range of non-human species, Vim and Vc receive excitatory input from the deep cerebellar nuclei, and from the dorsal column nuclei/spinal cord, respectively (Steriade et al. 1997;Sherman and Guillery 2001). To the contrary, primate and non-primate studies demonstrate that the analogs of human Vo receive GABAergic inputs from the internal pallidal segment. Therefore we expected to find lower firing rates, higher rates of LTS bursting and stronger pre-burst inhibition in Vo versus Vim and Vc. However, we observed the opposite.

Firing rates were higher and burst rates in Vo (Fig. 3a) were lower than in Vc, even when corrected for the primary event rate (Fig. 3b). The pre-burst ISI and ratio of pre-burst ISI/inverse of the primary event rate of neurons in Vo were not significantly different from the other nuclei. These results suggest that activity in Vo is driven by dense excitatory cortico-thalamic

inputs, while inhibitory pallidal inputs are modulators (Steriade et al. 1997; Sherman and Guillery 2001).

Studies in behaving animals have examined baseline firing rates and behaviorally significant activity in the pallidal INPUT receiving zone in monkey VLa corresponding to human Vo (Hirai and Jones 1989). The results demonstrate that neither baseline firing rates nor movement-related activity is dominated by inhibitory input (Anderson and Turner 1991). Modeling studies have also demonstrated that inhibitory inputs to the thalamus, like those from the internal pallidal segment to Vo, will not influence the neurons with firing rates of less than 50 Hz (Smith and Sherman 2002). Firing rates in the neurons of Vo were significantly less than 50 Hz, again suggesting that inhibitory input does not drive neuronal activity in Vo.

Significance of bursting

The present results contrast prior studies of the characteristics of spontaneous LTS bursts between functional classes within Vc. These classes were defined by the neuronal response to painful and non-painful, mechanical and thermal stimuli (Lee et al. 2005). There were no significant differences between LTS burst rates or between LTS bursts/principal event rates in different functional classes. Neither were there differences between the characteristics of spontaneous LTS associated inhibitory events in different functional classes (Lee et al. 2005). In all functional classes, the pre-burst ISIs were significantly greater than 100 ms, and the ratio of pre-burst ISI/inverse of the primary event rate were significantly greater than 1. Therefore, none of these measures of spontaneous inhibitory events was significantly different between functional classes in Vc. In contrast, the present study showed significant differences in these same measures between nuclei. Differences in LTS between human nuclei but not between neuronal functional classes within one nucleus may be a basic organizing principle for inhibitory circuitry and events within and between thalamic nuclei.

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References

Anderson ME, Turner DM (1991) Activity of neurons in cerebellar-receiving and pallidal-receiving areas of the thalamus of the behaving monkey. J Neurophysiol 66:879–893

Apkarian AV, Hodge CJ (1989) Primate spinothalamic pathways: III. Thalamic terminations of the dorsolateral and ventral spinothalamic pathways. J Comp Neurol 288:493–511

Cox DR, Lewis PAW (1966) The statistical analysis of series of events. Chapman and Hall, London

DeLong MR (1990) Primate models of movement disorders of basal ganglia origin. Trends Neurosci 13:281–285

Deuschl G, Bain P, Brin M (1998) Consensus statement of the Movement Disorder Society on Tremor. Ad Hoc Scientific Committee. Mov Disord 13(Suppl 3):2–23

Deuschl G, Krack P, Lauk M, Timmer J (1996) Clinical neurophysiology of tremor. J Clin Neurophysiol 13:110–121

Elble RJ (2002) Essential tremor is a monosymptomatic disorder. Mov Disord 17:633–637

Elble RJ, Koller W (1990) Tremor. Johns Hopkins University Press, Baltimore

Garonzik IM, Hua SE, Ohara S, Lenz FA (2002) Intraoperative microelectrode and semi-microelectrode recording during the physiological localization of the thalamic nucleus ventral intermediate. Mov Disord 17(Suppl 3):S135–S144

Hirai T, Jones EG (1989) A new parcellation of the human thalamus on the basis of histochemical staining. Brain Res Rev 14:1–34

Hua SE, Lenz FA (2005) Posture-related oscillations in human cerebellar thalamus in essential tremor are enabled by voluntary motor circuits. J Neurophysiol 93:117–127

Hua SE, Lenz FA, Zirh TA, Reich SG, Dougherty PM (1998) Thalamic neuronal activity correlated with essential tremor. J Neurol Neurosurg Psychiatr 64:273–276

Jahnsen H, Llinas R (1984a) Electrophysiological properties of guinea-pig thalamic neurones: an in vitro study. J Physiol 349:205–226

Jahnsen H, Llinas R (1984b) Ionic basis for the electro-responsiveness and oscillatory properties of guinea-pig thalamic neurones in vitro. J Physiol 349:227–247

Jankovic J (2002) Essential tremor: a heterogenous disorder. Mov Disord 17:638–644

Jeanmonod D, Magnin M, Morel A (1996) Low-threshold calcium spike bursts in the human thalamus. Common physiopathology for sensory, motor and limbic positive symptoms. Brain 119(Pt 2):363–375

Jenkins IH, Bain PB, Colebatch JG, Thompson PD, Findley LJ, Frackowiak RSJ, Marsden CD, Brooks DJ (1993) A positron emission tomography study of essential tremor: evidence of overactivity of cerebellar connections. Ann Neurol 34:82–90

Koller WC, Lyons KE, Wilkinson SB, Troster AI, Pahwa R (2001) Long-term safety and efficacy of unilateral deep brain stimulation of the thalamus in essential tremor. Mov Disord 16:464–468

Lee JI, Ohara S, Dougherty PM, Lenz FA (2005) Pain and temperature encoding in the human thalamic somatic sensory nucleus (ventral caudal): inhibition-related bursting evoked by somatic stimuli. J Neurophysiol 94:1676–1687

Lenz FA, Dougherty PM (1998) Cells in the human principal thalamic sensory nucleus (ventralis caudalis—Vc) respond to innocuous mechanical and cool stimuli. J Neurophysiol 79:2227–2230

Lenz FA, Kwan HC, Dostrovsky JO, Tasker RR (1989) Characteristics of the bursting pattern of action potentials that occurs in the thalamus of patients with central pain. Brain Res 496:357–360

Lenz FA, Kwan HC, Martin R, Tasker R, Richardson RT, Dostrovsky JO (1994) Characteristics of somatotopic organization and spontaneous neuronal activity in the region of the thalamic principal sensory nucleus in patients with spinal cord transection. J Neurophysiol 72:1570–1587

Lenz FA, Normand SL, Kwan HC, Andrews D, Rowland LH, Jones MW, Seike M, Lin YC, Tasker RR, Dostrovsky JO (1995) Statistical prediction of the optimal site for thalamotomy in parkinsonian tremor. Mov Disord 10:318–328

Lenz FA, Garonzik IM, Zirh TA, Dougherty PM (1998) Neuronal activity in the region of the thalamic principal sensory nucleus (ventralis caudalis) in patients with pain following amputations. Neurosci 86:1065–1081

Lenz FA, Jaeger CJ, Seike MS, Lin YC, Reich SG (2002) Single-neuron analysis of human thalamus in patients with intention tremor and other clinical signs of cerebellar disease. J Neurophysiol 87:2084–2094

McCarley RW, Benoit O, Barrionuevo G (1983) Lateral geniculate nucleus unitary discharge in sleep and waking: state and rate specific aspects. J Neurophysiol 50:798–818

Molnar GF, Pilliar A, Lozano AM, Dostrovsky JO (2005) Differences in neuronal firing rates in pallidal and cerebellar receiving areas of thalamus in patients with Parkinson's disease, essential tremor, and pain. J Neurophysiol 93:3094–3101

Ohara S, Lenz FA (2003) Medial lateral extent of thermal and pain sensations evoked by microstimulation in somatic sensory nuclei of human thalamus. J Neurophysiol 90:2367–2377

Perez-Reyes E (2003) Molecular physiology of low-voltage-activated t-type calcium channels. Physiol Rev 83:117–161

Radhakrishnan V, Tsoukatos J, Davis KD, Tasker RR, Lozano AM, Dostrovsky JO (1999) A comparison of the burst activity of lateral thalamic neurons in chronic pain and non-pain patients. Pain 80:567–575

Ramcharan EJ, Cox CL, Zhan XJ, Sherman SM, Gnadt JW (2000a) Cellular mechanisms underlying activity patterns in the monkey thalamus during visual behavior. J Neurophysiol 84:1982–1987

Ramcharan EJ, Gnadt JW, Sherman SM (2000b) Burst and tonic firing in thalamic cells of unanesthetized, behaving monkeys. Vis Neurosci 17:55–62

Schaltenbrand G, Bailey P (1959) Introduction to stereotaxis with an atlas of the human brain. Thiem, Stuttgart

Sherman SM, Guillery RW (2001) Exploring the thalamus and its role in cortical function. Oxford University Press, New York

Smith GD, Sherman SM (2002) Detectability of excitatory versus inhibitory drive in an integrate-and-fire-or-burst thalamocortical relay neuron model. J Neurosci 22:10242–10250

Steriade M, Jones EG, Llinas RR (1990) Thalamic oscillations and signaling. Wiley, New York

Steriade M, Jones EG, McCormick DA (1997) Thalamus organisation and function, vol 1. Elsevier, Amsterdam

Zirh AT, Lenz FA, Reich SG, Dougherty PM (1997) Patterns of bursting occurring in thalamic cells during parkinsonian tremor. Neurosci 83:107–121