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Research Report

Bursting activity of neurons in the human anterior thalamic nucleus

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AN, anterior nucleus
DM, dorsomedian nucleus
ISI, interspike interval
LTS, low-threshold calcium spike
TRN, reticular nucleus of the thalamus

ABSTRACT

Single unit microelectrode recordings were obtained under local anesthesia in 5 patients who underwent placement of deep brain stimulation electrodes in the anterior thalamic nucleus for control of intractable epilepsy. Of the 261 neurons recorded, 145 were in the anterior nucleus (AN), with the remainder ventral to AN in nucleus cucularis and dorsal dorsomedian nucleus (DM). 126 of the 261 neurons fired in bursts, and of these, 74 cells were analyzed in greater detail to characterize their bursting pattern. The bursts in 70% of the bursting neurons were characterized as low-threshold calcium spike (LTS) mediated bursts, on the basis of their intraburst firing pattern. The bursts of the remainder, although similar to LTS bursts, did not fulfil all of the criteria for an LTS burst and were termed atypical bursting cells. LTS and atypical bursting cells were found both within AN and in the nucleus cucularis and dorsal DM. The LTS bursting observed in these patients may be due to the altered electrophysiological state of the patients studied since LTS bursting in thalamus is usually only observed during sleep. This study describes for the first time the properties of this nucleus in humans and may be important in furthering our knowledge of thalamic mechanisms of epileptogenesis.

1. Introduction

The electrophysiological properties of neurons in the anterior nucleus of the thalamus (AN) have not been previously described in humans. This nucleus, located in the anteromedial region of thalamus, can be subdivided in the human into a large principal nucleus, termed anterior principalis by Hassler (1959) but is more commonly referred to in the animal literature as the anteroventral nucleus (Hirai and Jones, 1989) and smaller, accessory nuclei (anterior dorsal and anteromedial groups). The AN differs from most other thalamic nuclei in that it has extensive connections with the cingulate cortex, hippocampus, posterior hypothalamus and mammillary bodies, the latter providing its main afferent input.

Previous reports on the electrophysiology of thalamic neurons using extracellular and intracellular recordings have illustrated

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two key modes of cell firing: a bursting mode, primarily seen during slow wave sleep and drowsiness, and a tonic mode, observed during wakefulness (Swadlow and Gusev, 2001; Steriade et al., 1993, 1997). The burst firing of thalamic neurons during the burst mode is caused by low-threshold calcium spikes (LTS), which occur subsequent to de-inactivation of T-type calcium channels brought about by hyperpolarization of the cell membrane (Steriade et al., 1997). It is generally believed that LTS bursting does not occur in the fully awake animal, although there have been several reports of bursting activity in awake patients in both medial and lateral regions of thalamus (Lenz et al., 1989; Lenz et al., 1994; Jeanmonod et al., 1993; Radhakrishnan et al., 1999). Thus, it has been proposed that LTS bursting activity in the awake state is pathological and may contribute to or even cause the neurological symptoms (Lenz and Dougherty, 1997; Llinas et al., 1999), although this view is controversial (Radhakrishnan et al., 1999; Sherman and Guillery, 2006) and recent studies in the monkey have reported their existence also in the awake state especially in higher order nuclei (Ramcharan et al., 2005; Sherman and Guillery, 2006). It is also generally assumed that the bursting activity is usually rhythmic and synchronized.

The generation of spindling activity in thalamic neurons, in which LTS plays an important part, is thought to be mediated through connections with the reticular nucleus of the thalamus (TRN). The TRN has reciprocal GABAergic connections with most thalamic nuclei and shows specific electroencephalographic appearance of synchrony in spindle rhythms (Steriade et al., 1997). In keeping with this observation, experiments in the cat have illustrated that nuclei that lack connectivity to the TRN, such as the AN (in the cat), do not show evidence of spindling activity (Pare et al., 1987). However, more recent works in the rat and monkey suggest that at least in these species the AN does have reciprocal connections with the TRN (Gonzalo-Ruiz and Lieberman, 1995; Kultas-Ilinsky et al., 1995; Radhakrishnan et al., 1999; Shibata, 1992).

Animal studies have suggested that the AN may have an important role in seizure mechanisms. These include increased metabolic activity in AN during seizures (Mirski and Ferrendelli, 1986) and that interventions in AN or its afferents, including lesioning (Mirski and Ferrendelli, 1987) or high frequency stimulation (Mirski and Fisher, 1994), reduce seizure activity in models of epileptogenesis in experimental animals. We have therefore conducted a pilot study that examined the effects of chronic deep brain stimulation (DBS) in the AN of a group of patients with intractable seizures. This study has provided us with a unique opportunity to examine the firing properties of cells of the anterior thalamic nucleus in humans using intraoperative microelectrode recordings prior to implantation of the DBS electrodes. The aim of this project is two-fold: to describe the specific electrophysiological properties of the neurons of the anterior thalamic nucleus and to investigate the possibility of establishing specific electrophysiological criteria that would define the anterior nucleus neurons to facilitate target localization intraoperatively.

2. Results

The microelectrode path to the AN traversed the white matter tracts of the corpus callosum and the lateral ventricle. Below the ventricle, the AN was encountered as evidenced by increased background noise and the presence of somatodendritic action potentials. Along this trajectory, posteroventral to the anterior nucleus, a small nucleus, the nucleus cucularis (identified as dorsomedial central lateral nucleus by Hirai and Jones (1989)) is encountered followed by the dorsomedian nucleus (DM; see Fig. 1). There was no consistent and easily identifiable boundary between the nuclei, and so it was not possible to determine precisely which neurons were in each of the three nuclei.

The first cells were generally encountered at a different depth for each patient, ranging from 3 mm above target to 4 mm below target, and this difference is presumably due primarily to the limited resolution of the imaging based coordinates of the AC and PC and differences between the patients' thalamic anatomy and the standard stereotaxic atlas coordinates for the AN.

The locations and initial assessment of firing pattern were determined for 261 neurons recorded in 12 electrode penetrations (tracks) in 5 patients. Of these, 145 were recorded within 5 mm of the first neuronal recording and assumed to be in AN. On the basis of visual inspection of the firing pattern, 126 of the 261 neurons (48%) fired in bursts that resembled LTS bursts. Fig. 2 shows an example of a cell firing in bursts. Two bursts are shown in the trace on the left, and on the right is an expanded view of the first burst shown on the left. The bottom trace is the raw recording, the top trace shows the waveforms of the discriminated spikes and beneath these the events representing the discriminated spikes are indicated by vertical bars and beneath these the tracing shows the output of the automated burst identification script.

Fig. 3A shows the distribution of the bursting cells as a function of depth in 1 mm bins. In this histogram, we used the first cell encountered as the electrode entered the thalamus as a reference point and arbitrarily assigned its position as 5 mm above the ventral border of the AN (the target) since according to the Schaltenbrand and Wahren (1977) atlas, this corresponds to the span of AN in our typical trajectories. Fig. 3B plots the percentage of bursting cells at each 1 mm interval and reveals that the percentage was roughly the same (about 50%) at each depth. Change point analysis did not reveal any significant changes in incidence of bursting cells with depth. 74 of the bursting neurons fulfilled the criteria of good signal-to-noise ratio and adequate length of recording and were studied in detail. These bursting cells characteristically had a long mean burst duration (average = 11.7 ± 2.8 ms), with the number of spikes per burst ranging between 2 and 8, however in 43% of the cells, the number of spikes per burst was higher than 8 for some bursts. The values for pre-burst interval ranged between 146 and 363 ms. Autocorrelogram analysis revealed that only 7 of these cells had a rhythmic bursting activity, which ranged from 2 to 5 Hz. We found no relationship between bursting activity and the patients' state of wakefulness or sleep as assessed by visual inspection of the patient. However, EEG recordings were not available, and thus more rigorous analysis of a possible relationship with sleep state could not be performed.

The detailed analysis of intraburst firing pattern revealed two types of bursting neurons. In the first type, the intraburst firing pattern had the same characteristics as those known to

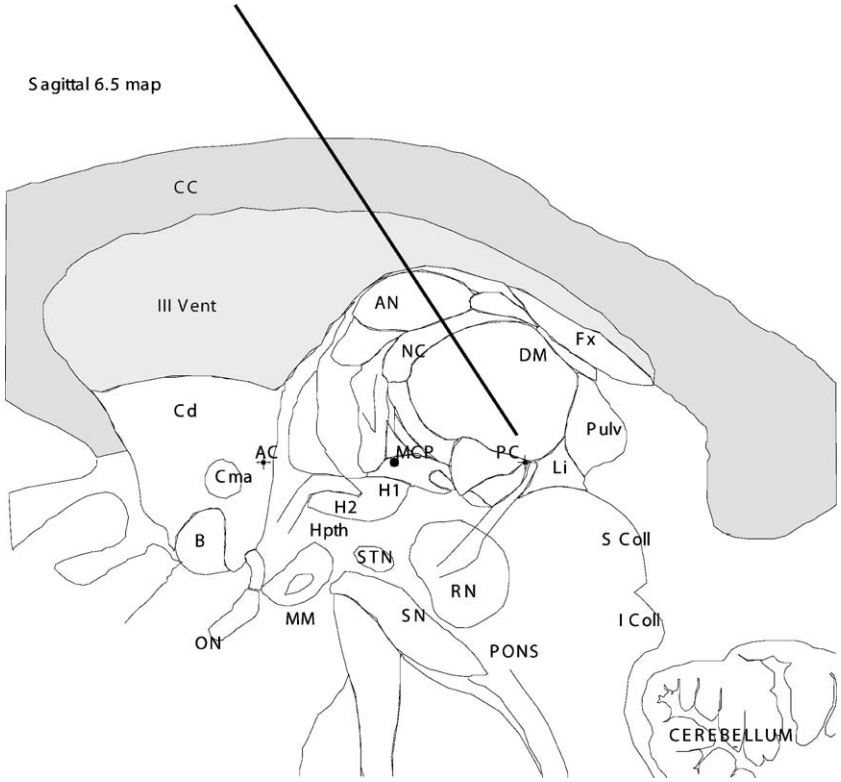

Fig. 1 – Schaltenbrand and Wahren atlas section 6.5 mm in the sagittal plane, showing a typical electrode trajectory through the anterior thalamic nucleus. Legend: AC: anterior commissure; AN: anterior nucleus; B: Nucleus basalis; CC: corpus callosum; Cd: caudate nucleus; Cma: anterior commissure; DM: dorsomedian nucleus; Fx: fornix; H1, H2: fields of Forel; Hpth: hypothalamus; IColl: inferior colliculus; Ll: lemniscus lateralis; MM: mammillary bodies; NC: nucleus cucularis; ON: optic nerve; PC: posterior commissure; Pulv: pulvinar; RN: red nucleus; SColl: superior colliculus; SN: substantia nigra; STN: subthalamic nucleus; IIIVent: third ventricle.

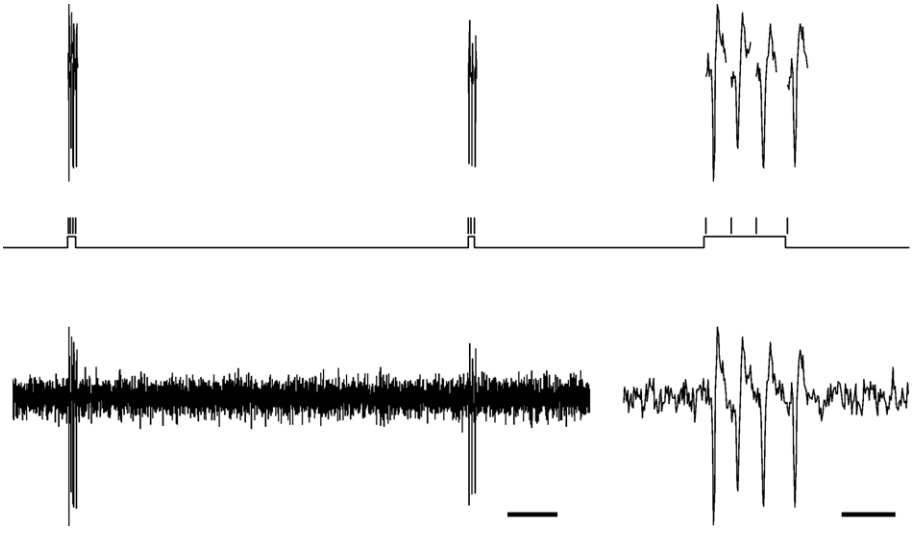

Fig. 2 – An example of a cell firing in bursts. Two bursts are shown in the trace on the left, and on the right is an expanded view of the first burst shown on the left. The bottom trace is the raw recording, the top trace shows the waveforms of the discriminated spikes and beneath these the events representing the discriminated spikes are indicated by vertical bars and beneath these the tracing shows the output of the automated burst identification script. Scale bar on left—50 ms, on right—5 ms.

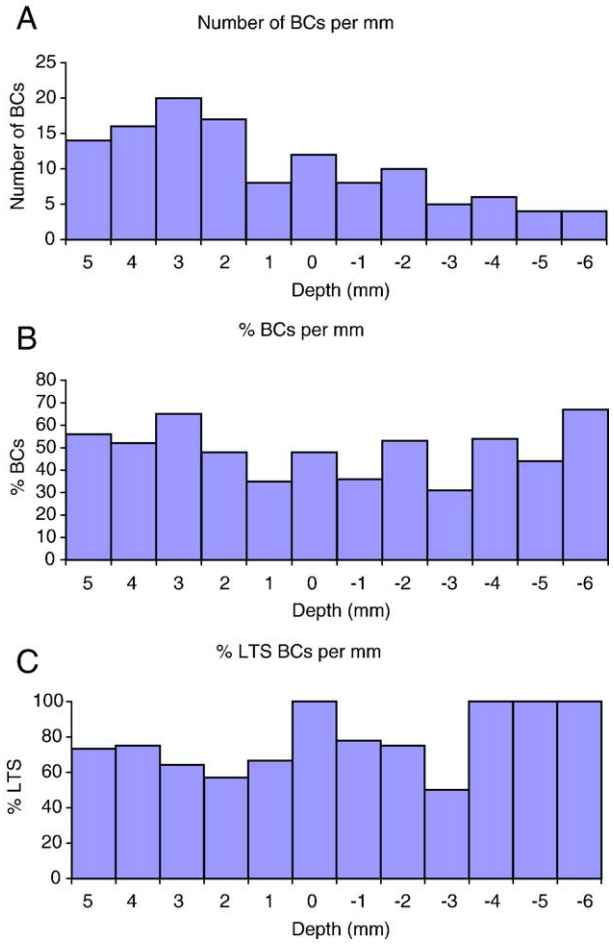

Fig. 3 – Histograms showing the distribution of bursting cells by depth along the electrode track. Data have been pooled from all 5 patients and calculated in 1 mm intervals. In these histograms, the depth of the first cell encountered as the electrode entered the thalamus in each patient was used as a reference point, and arbitrarily assigned a depth of 5 mm above the ventral border of the AN (the target), since according to the Schaltenbrand and Wahren (1977) atlas, this corresponds to the span of AN in our typical trajectories (see Fig. 1). The top panel, A, shows the distribution of the bursting cells as a function of depth. Panel B plots the percentage of bursting cells of the total number of cells recorded in each 1 mm interval. Panel C plots the percentage of the bursting cells which were classified as LTS.

arise from a low-threshold calcium spike. These constituted the majority of the bursting cells encountered (53 out of 74 cells, or 72%). These cells met all the described criteria for low-threshold calcium spike mediated bursts as described in the Experimental procedures section. An example of the intraburst firing pattern for one of these cells is shown in Figs. 4A and B. We have termed this bursting activity as LTS bursting. The second type of bursting fulfilled some but not all the criteria for low-threshold calcium spikes (21 out of 74 cells, or 28%). The graphs of interspike interval vs. burst size were atypical, reflecting the fact that the successive intervals within bursts did not consistently increase and that the first ISI did not decrease with increasing burst size (see example in Figs. 4C, D).

The details of the burst characteristics for these two types of bursting neurons are shown in Tables 1 and 2. No significant difference was found between the two burst types with respect to mean burst duration and mean number of spikes per burst. However, the pre-burst interval was significantly shorter for the atypical bursts as compared with the LTS (143.8 ms for atypical bursts, vs. 224.9 ms for LTS bursts). LTS type bursts were found at all depths as can be see from Fig. 3C which plots the percentage of the bursting cells which were classified as LTS as a function of depth along the electrode track.

High frequency microstimulation at up to 100 μA in these structures was not found to cause any clinical or behavioral effect (sensations or movements).

3. Discussion

This is the first report of the firing properties of neurons in the AN of awake patients. Of particular interest was the finding that many of the neurons fired in short high frequency bursts. However, similar bursting activity was found also in the underlying nucleus cucularis and dorsal DM and is thus not unique to AN. The bursting activity may represent a normal property of the neurons in this region in the awake human or due to pathology and/or the medications (see further discussion below).

Detailed analysis of the bursting activity revealed that in about 70% of the neurons the bursts had the characteristic pattern associated with an underlying calcium spike, namely increasing ISIs for successive spikes within a burst, a smaller initial ISI for larger burst sizes, and long pre-burst intervals (Sherman and Guillery, 2006; Steriade et al., 1997; Radhakrishnan et al., 1999). However, in the other 30% of neurons, not all of these characteristics were consistently present, suggesting that they may be produced by a different mechanism. However, in the absence of intracellular recordings, we cannot definitively conclude that the bursts of the LTS group are indeed due to a calcium spike or provide an explanation for the cause of the atypical bursts which may also involve T-type calcium channels.

LTS type bursting in the thalamus is generally believed to occur only during drowsiness and sleep (Steriade et al., 1993, 1997). Thus, the occurrence of LTS bursting in these patients who were awake during the recordings may be abnormal and due to the underlying pathology or medications. Similar bursting activity has been reported previously in several other thalamic nuclei in awake patients and was attributed to pathology (Lenz et al., 1989, 1994; Jeanmonod et al., 1993; Radhakrishnan et al., 1999), and indeed it has been proposed that thalamic bursting may be involved in epilepsy (Buzsaki et al., 1990). The patients in this study suffered from severe epilepsy and were under medication at the time of surgery. Thus, it is possible that one or both of these factors depressed excitatory inputs and/or increased inhibition leading to membrane hyperpolarization sufficient to cause the thalamic neurons to go into the bursting state. It is known that LTS bursts can occur following inhibitory post-synaptic potentials

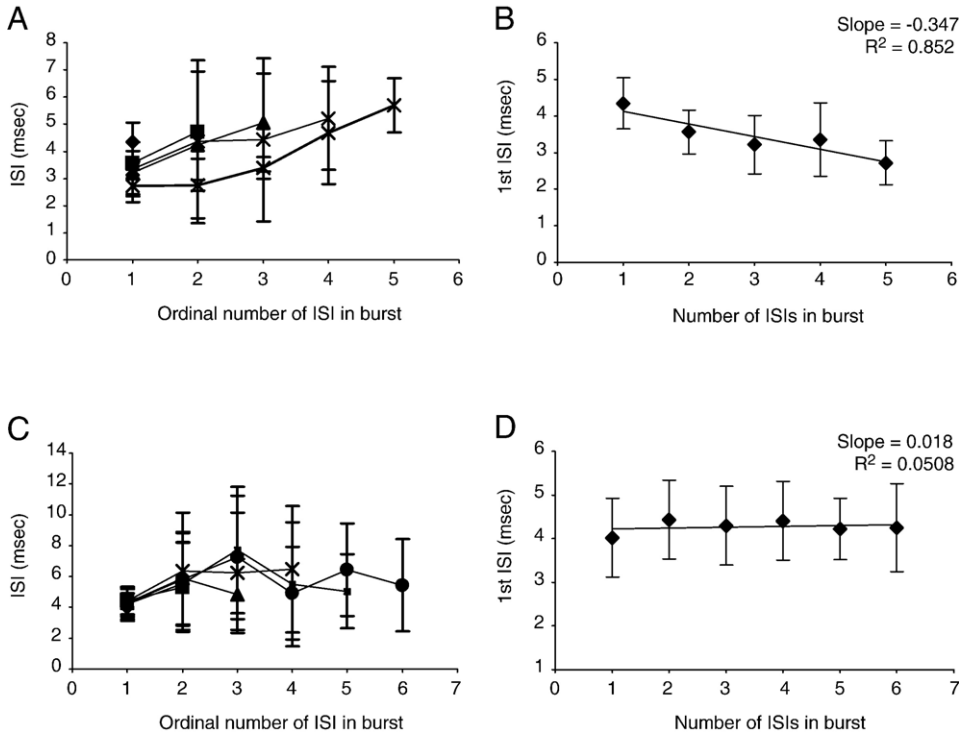

Fig. 4 – Examples of LTS and atypical bursting. Graph A: plot of interspike intervals (ISIs; ms) against the ordinal number of the ISI within the burst showing the characteristic increase in the successive ISIs within a burst. Graph B: plot of the first ISI against the number of ISIs in the burst for the cell in A showing the progressive decrease in the ISI with increasing burst size and the inverse relationship between the number of spikes in the burst and the duration of the first interspike interval. Graph C: plot of ISIs as a function of ordinal number of ISI for an atypical bursting cell. Graph D: Plot of first ISI against number of ISIs in the burst for the cell shown in C.

(Steriade et al., 1997), which are generated in the cat AN following low frequency (≤0.5 Hz) stimulation of the mammillary body in a mechanism likely mediated by $GABA_A$ receptors (Pare et al., 1991), illustrating the role of the mamillothalamic tract or interneurons in this process. It is possible that increased activity in this pathway may contribute to the patients' susceptibility to seizures since lesioning of the mammillary bodies in the rat leads to decreased seizure activity in pentylenetetrazol (PTZ) treated animals. Since all of the patients had a long-standing history of seizure disorder, it is possible that the bursting activity is a consequence of aberrant mammillothalamic and/or cortico-thalamic activity or potentially a result of long term anticonvulsant use. Although further evidence is necessary to establish a causal relationship between AN bursting cells and seizures, it is possible that AN bursting cells may represent an altered inhibitory milieu that is facilitatory for seizure propagation.

On the other hand, in the absence of recordings from normal control subjects, we cannot rule out the possibility that bursting activity in this region in the awake human is a normal characteristic (see Sherman and Guillery, 2006; Radhakrishnan et al., 1999), despite the generally held view that such activity only occurs during sleep (Steriade et al., 1993). In support of this view are recent reports of bursting activity in the awake monkey and showing that they are particularly common in higher order nuclei such as central medial (Ramcharan et al., 2005). Although AN is considered to be a first order thalamic relay nucleus (Sherman and Guillery,

Table 1 – Characteristics of different burst types encountered in the AN region — LTS

Patient	# cells	Number of bursts	Mean burst duration (ms)	Mean pre-burst interval (ms)	Mean number of spikes per burst	% Spikes per burst
1	11	1209	16.1±15.4	172.5±147.7	4.9±4.6	45.0±28.2
2	14	797	10.7±3.7	228.8±100.4	3.3±0.9	42.8±20.5
3	7	565	12.6±3.6	146.3±114.7	3.7±0.6	50.8±15.6
4	18	905	8.6±2.1	361.7±373.9	2.9±0.4	38.0±12.9
5	3	146	10.5±3.7	215.1±85.5	3.5±1.1	49.0±33.1
Totals/Averages	53	3622	11.7	224.9	3.7	45.1

Table 2 – Characteristics of different burst types encountered in the AN region — atypical bursting cells

Patient	# cells	Number of bursts	Mean burst duration (ms)	Mean pre-burst interval (ms)	Mean number of spikes per burst	% Spikes per burst
1	5	290	11.5±6.5	127.8±108.7	3.1±1.1	35.6±31.4
2	3	121	9.4±3.5	282.4±149.8	3.1±0.8	46.5±10.5
3	3	233	12.3±5.1	79.9±53.7	3.2±0.7	38.4±7.6
4	7	492	11.1±4.9	169.7±191.9	3.2±0.9	35.3±17.0
5	3	250	14.8±6.2	59.3±47.9	3.4±0.7	39.5±8.1
Totals/Averages	21	1386	11.8	143.8	3.2	39.1

2006), the incidence of bursting was found to be similar to that in the underlying higher order relay nuclei and may suggest that at least in this respect the AN is not a typical first order relay nucleus. Furthermore, in the absence of concurrent EEG recordings, we cannot rule out the possibility that some of the bursting occurred during drowsiness.

In contrast to the bursting observed during sleep, which tends to occur during spindling and is rhythmic, the bursting observed in these patients was not associated with spindling activity and in most cases was not rhythmic. In the few cases displaying some rhythmicity, the autocorrelograms revealed only weak oscillatory activity in contrast to the very pronounced rhythmic activity reported by Jeanmonod in the centralis lateralis nucleus (Jeanmonod et al., 1996; Magnin et al., 2000) and rhythmic bursting activity we have detected in about 30% of ventrally located DM neurons recorded in awake pain patients (Cordella and Dostrovsky, unpublished observations).

Bursts were categorized as atypical when all the criteria for LTS generated bursts were not met. In these cells, there was no consistent progressive lengthening of the intervals between successive spikes within the burst and/or no decrement in the first ISI with increasing number of spikes in the burst. About 30% of the bursting neurons were of this type. The properties of the bursts in these cells were, however, very similar to those of the classical LTS burst in that ISIs within the burst were comparable, as was burst duration. Since the categorization into typical or atypical was based on the average data from all of the bursts recorded in a given cell, we cannot comment on whether in these cells there was a mixture of normal and atypical bursts such as was observed in recordings done in Parkinsonian patients in the centralis lateralis and lateral thalamus by Magnin et al. (2000). Magnin et al. (2000) reported finding that about 22% of the bursts in any given LTS bursting neuron consisted of a longer first ISI but that the rest of the burst had the typical pattern. The cells identified as atypical in our study resembled those classified as decelerating in a study by Zirh et al. (1998). In their study, 16% of the cells in the lateral thalamus of Parkinsonian patients were found to fire in bursts which were similar to those of LTS bursting neurons except that the first interspike interval remained relatively constant regardless of train length. The significance of the atypical bursting cells is not clear. It is possible that they represent a subpopulation of neurons under a different influence or with altered cell membrane properties so as to allow the generation of an atypical burst pattern.

4. Experimental procedures

The study protocol was approved by our institutional ethics board. Informed consent was obtained from the patients' guardians. Microelectrode recordings were carried out intraoperatively on 5 patients who underwent insertion of DBS electrodes in the AN for epilepsy (Table 3). Patient ages ranged from 19 to 45, with duration of disease between 18 and 44 years. The patients were on their standard anti-epileptic drugs (see Table 3) at the time of their operative procedure but did not receive additional drugs during the procedure. The clinical effects of deep brain stimulation for epilepsy in these patients have been published elsewhere (Hodaie et al., 2002).

Table 3 – Demographics and clinical characteristics of the patients with DBS for epilepsy

Patient	Age	Age of seizure onset	Sex	Seizure type	Epilepsy classification	Anticonvulsant medication
1	45	1 years	F	GTC	Symptomatic generalized	Topiramate, Carbamazepine, Clonazepam, Valproic acid
2	36	2 years	F	GTC	Symptomatic generalized	Phenytoin, Valproic acid, Lorazepam
3	22	1 years	M	Atonic drop attacks, complex partial vs. atypical absence, GTC	Multifocal vs. symptomatic generalized	Carbamazepine, Vigabatrin
4	30	5 years	F	Complex partial, secondarily GTC	Partial with secondary generalization; right frontal maximum	Carbamazepine, Topiramate, Lamotrigine
5	19	1 years	M	Partial motor, secondarily GTC	Multifocal/partial with secondary generalization; bifrontal, right>left	Valproic acid, Nitrazepam, Phenytoin

GTC: generalized tonic clonic seizures.

4.1. *Operative approach and thalamic microrecordings*

Patients underwent preoperative magnetic resonance imaging (MRI) using a Leksell frame for stereotactic determination of targets and the anterior commissure/posterior commissure (AC/PC) line as reference. Surgery was performed under local anesthesia with microelectrode recording guidance. Details of microelectrode recordings are similar to those done in stereotactic procedures such as for Parkinson's disease and have been previously published (Lozano et al., 1996). Briefly, extracellular recordings were made using tungsten microelectrodes, through bilateral burr holes drilled in the prefrontal area. Neuronal activity was recorded throughout the trajectory towards the target and typically spanned a distance of 10 mm above the target to 10 mm below it. The targets were chosen as 6.0 mm from the midline on the sagittal plane and 12 mm superior to AC/PC line and 8 mm anterior to the posterior commissure, using the Schaltenbrand and Wahren (1977) atlas.

Neuronal recordings were amplified, filtered (300 to 5 k Hz bandpass) and displayed using the Guideline System 3000 (Axon Instruments, CA). Concurrent audio and video recordings were made throughout the microelectrode recordings. This allowed the assessment of the sleep–wake status of the patients and to temporally correlate the findings to specific cells encountered. Neuronal activity was stored on tape and analyzed further off-line.

4.2. *Data analysis*

Neuronal recordings were replayed using the CED 1401-plus data acquisition system and the Spike2 package (Cambridge Electronic Devices, Cambridge, UK). All bursting neurons with a good signal-to-noise ratio and recordings of longer than 20 s which appeared stable and did not contain an injury discharge were analyzed. Single units were discriminated using a BAK dual window discriminator or the 'wavemark' template matching software supplied with Spike2 (see Fig. 2 top traces).

Cells that fired in bursts were studied quantitatively to determine the burst characteristics. The inter- and intraburst firing patterns were automatically analyzed by a burst script written for Spike2. For this purpose, the bursts had to fulfil the following criteria (Tsoukatos et al., 1997): minimum pre-burst interval=20 ms; maximum interval between first two spikes of burst=6 ms; maximum interval between spikes in any one burst=15 ms; minimum interval between first two spikes in burst=2 ms; minimum number of spikes per burst=2. The bursts identified by the script were frequently verified by comparing the identified bursts with the spike train displayed immediately beneath (see Fig. 2). The various parameters provided by the script were imported into a spreadsheet and graphics packages (Excel software, Microsoft, WA) for further analysis. The durations of consecutive interspike intervals (ISIs) within each burst were determined for each cell. These values were then used to construct plots of mean ISIs as a function of the ordinal position of the ISI in the burst for each burst size and of the mean first ISIs as function of the number of ISIs in the burst. An LTS mediated burst was identified if it fulfilled the abovementioned burst criteria as well as the following two criteria: (a) the first ISI was smaller with larger burst size (more spikes per burst), and (b) successive ISIs within a given burst increased. These properties were assessed and verified according to the methods described in Radhakrishnan et al. (1999). Cells that did not fulfil the latter two criteria were considered as atypical burst cells. Firing rhythmicity was assessed by autocorrelogram analysis of the spike train.

Microelectrode trajectories were reconstructed based on calculated stereotactic coordinates and projections onto the specific atlas map. Cells were assigned to a particular thalamic nuclear division according to their depth below the dorsal border of AN as determined by the increase in background noise and/or the first recording of neuronal firing. The recording sites of the neurons for each patient were then transferred to produce a composite map. All patients underwent postoperative MR or CT imaging, which verified the placement of the DBS electrode in the region of the anterior thalamus.

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