

The subthalamic nucleus in Parkinson's disease: somatotopic organization and physiological characteristics

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Summary

Single-cell recording of the subthalamic nucleus (STN) was undertaken in 14 patients with Parkinson's disease submitted to surgery. Three hundred and fifty neurones were recorded and assessed for their response to passive and active movements. Thirty-two per cent were activated by passive and active movement of the limbs, oromandibular region and abdominal wall. All neurones with sensorimotor responses were in the dorsolateral region of the STN. Arm-related neurones were lateral (≥ 14 mm plane) to leg-related neurones, which were found more medially (≤ 12 mm). Representation of the oromandibular musculature was in the middle of the sensorimotor region (~ 13 mm plane) and ventral to the arm and leg. Two hundred neurones were adequately isolated for 'off-line' analysis. The mean frequency of discharge was 33 ± 17 Hz (13–117 Hz). Three types of neuronal discharges were distinguished: irregular (60.5%), tonic (24%) and oscillatory (15.5%). They were statistically differentiated on the basis of their mean firing frequency and the coefficient of variation of the interspike interval. Neurones responding to movement were of the irregular or tonic

type, and were found in the dorsolateral region of the STN. Neurones with oscillatory and low frequency activity did not respond to movement and were in the ventral one-third of the nucleus. Thirty-eight tremor-related neurones were recorded. The majority (84%) of these were sensitive to movement and were located in the dorsolateral region of the STN. Cross power analysis ($n = 16$) between the rhythmic neuronal activity and tremor in the limbs showed a peak frequency of 5 Hz (4–8 Hz). Neuronal activity of the substantia nigra pars reticulata was recorded 0.5–3 mm below the STN. Eighty neurones were recorded 'on-line' and 27 were isolated for 'off-line' analysis. A tonic pattern of discharge characterized by a mean firing rate of 71 ± 28 Hz (35–122 Hz) with a mean coefficient of variation of the interspike interval of 0.85 ± 0.29 ms was found. In only three neurones (11%) was there a response to sensorimotor stimulation. The findings of this study indicate that the somatotopic arrangement and electrophysiological features of the STN in Parkinson's disease patients are similar to those found in monkeys.

Keywords: subthalamic nucleus; Parkinson's disease; somatotopic organization; neuronal activity; tremor-related neurones

Abbreviations: CV = coefficient of variation; DBS = deep brain stimulation; GPI = globus pallidus lateralis; GPM = globus pallidus pars medialis; ISI = interspike interval; STN = subthalamic nucleus; SNpr = substantia nigra pars reticulata

Introduction

The subthalamic nucleus (STN) is currently thought to play a prominent role in the pathophysiology of Parkinson's disease (Obeso *et al.*, 1997a). Metabolic, electrophysiological and behavioural studies performed mainly in the MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-monkey model of Parkinson's disease revealed an increase in neuronal activity of the subthalamic nucleus and the main output basal ganglia nuclei, the globus pallidum pars medialis (GPM) and substantia nigra pars reticulata (SNpr) (Mitchell *et al.*, 1989; Bergman *et al.*, 1994; Herrero *et al.*, 1996; Vila *et al.*, 1996, 1997). The role of STN hyperactivity in the parkinsonian syndrome was demonstrated in MPTP monkeys by showing that a unilateral lesion was accompanied by a dramatic improvement in motor features such as akinesia, rigidity, freezing of gait and postural tremor (Bergman *et al.*, 1990; Aziz *et al.*, 1991; Guridi *et al.*, 1996). Such a clinical effect was associated with a reduction in the expression of mRNA for glutamic acid decarboxylase (GADmRNA), a rate-limiting enzyme for GABA synthesis (Guridi *et al.*, 1996), and neuronal firing rate in the GPM and SNpr (Wichmann *et al.*, 1994a). These experimental findings, plus the limitations of existing pharmacological treatments, led to a resurgence of stereotactic surgery for Parkinson's disease (Laitinen *et al.*, 1992; Vitek and Bakay, 1997; Obeso *et al.*, 1997b).

The somatotopic organization of the STN has been described in the normal monkey. Anatomical and electrophysiological studies coincided in localizing the sensorimotor region in the dorsolateral portion of the STN (Monakow *et al.*, 1978; DeLong *et al.*, 1985; Wichmann *et al.*, 1994b; Nambu *et al.*, 1996, 1997). Somatotopically organized projections from neurones labelled with anterograde markers in the primary motor cortex (Monakow *et al.*, 1978) and neurones, which increased their frequency of discharge in response to passive movements (DeLong *et al.*, 1985; Wichmann *et al.*, 1994a), were found in the dorsolateral region of the STN. Within this region, the leg area appears to lie medial to the arm area and the face representation is in the most lateral zone of the nucleus (DeLong *et al.*, 1985; Wichmann *et al.*, 1994a; Nambu *et al.*, 1996).

In patients with Parkinson's disease, Hutchison and colleagues found a mean firing rate of 37 ± 17 Hz and a predominant irregular firing pattern in the STN (Hutchison *et al.*, 1998). They also identified a number of neurones responsive to movements and tremor-related cells, but did not describe the somatotopic organization of the nucleus. Recently, Magariños-Ascone and colleagues reported the firing characteristics of STN neurones in parkinsonian patients (Magariños-Ascone *et al.*, 2000). They identified three main types of discharge patterns: tonic, phasic and rhythmic discharges, with a firing rate ranging between 59 and 69 Hz. In the present physiological study of the STN in Parkinson's disease, we have classified neuronal activity according to the pattern of discharge, assessed the somatotopic arrangement

and analysed the relationship between neuronal activity and movement and tremor of the limbs.

Patients and methods

We have recorded neuronal activity from the STN during surgery for implantation of electrodes for deep brain stimulation (DBS) in 14 patients with Parkinson's disease carried out in Clinica Quiron (San Sebastian) and Hospiten (Tenerife), Spain. Fifty-seven recording tracks were performed in 25 subthalamic nuclei. A total of 350 neurones were recorded with a mean of 14 neurones per nucleus. All patients had idiopathic Parkinson's disease according to the Brain Bank Criteria (Gibb and Lees, 1988) with a positive response to levodopa and major motor complications such as 'on-off' fluctuations and dyskinesias related to treatment with dopaminergic drugs. The protocol was approved by the Spanish Government Ministry of Health and patients' consent was obtained according to the declaration of Helsinki.

Surgical procedure and electrophysiology

Standard stereotactic methods were used to localize the STN. Imaging acquisition was performed using MRI (0.5 T; General Electric, Germany; 19×192 matrix), and afterwards, the stereotactic frame (Leksell G model) was placed under local anaesthesia. The MRI software provided the distance between the anterior and the posterior commissures in relation to the centre of the stereotactic frame. These data were transcribed to the digitized version of the stereotactic atlas of Shaltenbrand and Wahren (Shaltenbrand and Wahren, 1977). These atlas images were adjusted making them coincide with the length of the intercommissural line of the patient. The theoretical coordinates to target the STN were: 11–13 mm lateral to the intercommissural line, 4–6 mm below this line and 2–3 mm behind the mid-intercommissural point.

Microrecording using platinum–iridium microelectrodes (tip diameter $< 10 \mu\text{m}$, impedance of 0.2–0.5 M Ω at 1000 Hz) were used for extracellular single unit and multi-unit neuronal recording (DeLong *et al.*, 1985; Vitek *et al.*, 1998). A DAM-80 preamplifier and a BAK dual oscilloscope were used to amplify, filter (300–2000 Hz) and display the signals. Units were isolated 'on-line' by a window discriminator. The system was connected to an audio-amplifier which allowed auditory recognition of the different neuronal discharge patterns. The same electrode used for recording allowed microstimulation (10–100 μA , 0.2–0.5 ms pulse duration at 300 Hz).

Recording tracks were made in a parasagittal plane with a 45–60° angle with respect to the horizontal plane of the stereotactic frame. The microelectrode was advanced 20 mm with a macromanipulator, and the last 25–35 mm with a hydraulic microdrive. The neuronal activity recorded was used to identify the structures dorsal to the STN. Parallel

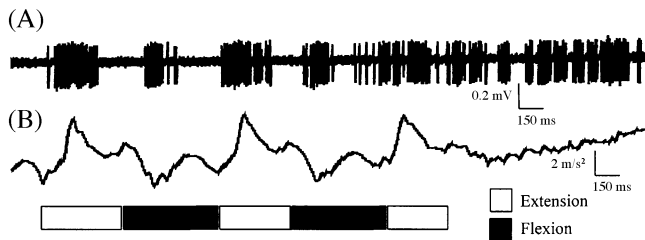


Fig. 1 Single cell recording of a neuron (A) of the STN during passive extension, and flexion movements of the wrist recorded with an accelerometer (B). Neuronal discharges are observed following either extension or flexion displacement. Once the manipulation was halted (last segment of the trace) the neurone reassumed its spontaneous activity.

recording tracks in the parasagittal plane were performed to define the sensorimotor region of the STN and its boundaries.

Neuronal activity of a typical recording track corresponds initially to the striatum (caudate nucleus) followed by low amplitude fibre activity while passing through the internal capsule. Thalamic activity, corresponding to the reticular nucleus, is recorded when an angle of 50–60° is used and when the track is relatively caudal. Approximately 1–3 mm before reaching the STN, electrical activity increases due to medium size (50–200 μ V) fibre potentials, possibly corresponding to Forel's fields. Upon entering the STN, a robust increase in neuronal activity is encountered, with multiple units discharging at relatively high frequency. Such activity may be recorded between 1 and 7 mm, depending on the relative position of the recording electrode in the mediolateral and rostrocaudal planes of the STN. The bottom of the nucleus is indicated by the reduction in the number of active neurones followed by electrical silence for ~0.5–3 mm depending on the laterality. This is followed by tonic, high frequency neuronal activity, which corresponds to the SNpr.

Neurones were recorded in rest condition (patient not moving voluntarily or passively) for 30–60 s. Subsequently, the same neurones were recorded during both passive and active movements of the limbs, face, tongue, mouth muscles and abdominal wall. The sensorimotor region of the nucleus was thus defined by the presence of clear-cut increments in neuronal activity in response to activation manoeuvres (Fig. 1). Patients were generally asked to move voluntarily the wrist, arm, shoulder, leg and foot and any other segment where passive activation elicited neuronal responses.

Electromyographic activity of the tibialis anterior and extensor carpi radialis of the limbs was recorded using surface silver–silver electrodes simultaneously with the neuronal recording. Both the neuronal and electromyographic signals were stored for 'off-line' analysis. Every neurone with 'sensorimotor' responses was noted intra-operatively and referred to its relative position in the track using the mediolateral and dorsoventral planes (coordinates x and z). Each recording track within the STN was divided in the dorsoventral plane (z stereotactic coordinate) into three equal segments referred to as: dorsal, middle and ventral. Similarly,

Table 1 Somatotopic distribution of movement-related neurones ($n = 111$) in the dorsoventral axis of the subthalamic nucleus

	Dorsal segment	Middle segment	Ventral segment
Leg	35 (90%)	4 (10%)	0
Arm	41 (77%)	12 (23%)	0
Face	8 (50%)	8 (50%)	0
Abdomen	3	0	0
Total	87 (78.3%)	24 (21.6%)	0 (0%)

Table 2 Somatotopic distribution of movement-related neurones ($n = 111$) in the mediolateral axis of the subthalamic nucleus

	≤ 12 mm	12–14 mm	≥ 14 mm
Leg	20 (51%)	16 (41%)	3 (8%)
Arm	12 (23%)	16 (30%)	25 (47%)
Face	2 (12.5%)	12 (75%)	2 (12.5%)
Abdomen	1 (33%)	1 (33%)	1 (33%)
Total	35 (31.5%)	45 (40.5%)	31 (28%)

the nucleus was divided into three mediolateral portions (x stereotactic coordinate) with respect to the AC–PC (anterior–posterior commissure) line as follows: (i) laterality ≤ 12 mm; (ii) lateral > 12 and < 14 mm; and (iii) laterality ≥ 14 mm. Planes' lateralities were calculated taking as objective reference the mediolateral location of the DBS electrode, assessed by MRI postoperatively. This value was then matched with the x coordinate used during surgery to place the DBS electrode, and the rest of planes explored physiologically were readjusted accordingly. Admittedly, the accuracy of this method is limited by the resolution capacity and imaging distortion of the MRI; however, all patients' electrophysiological findings and MRI were assessed identically, thus maintaining relatively constant whatever degree of variability was introduced by the imaging process.

Analysis of neuronal activity and statistics

Neuronal action potentials were discriminated using the AlphaSort program (Alpha Omega software). Well-isolated neurones were digitized for analysis with the Labview program. This program provides quantitative information about the activity of a single neurone during a 12 s period. Statistics derived from the analysis included the interspike interval (ISI) histogram and instant frequency histogram with a temporal basis of 50 ms, mean firing rate, the minimum and maximum ISI and the burst index. A one-way analysis of variance with *post hoc* exploratory evaluation (Scheffe's test) was used for differences in firing rate and the coefficient of variation (CV) of the ISI for each neuronal type.

In patients in whom tremor was a prominent feature, microrecording of the neuronal activity in the STN, and electromyographic study of the muscles involved in the

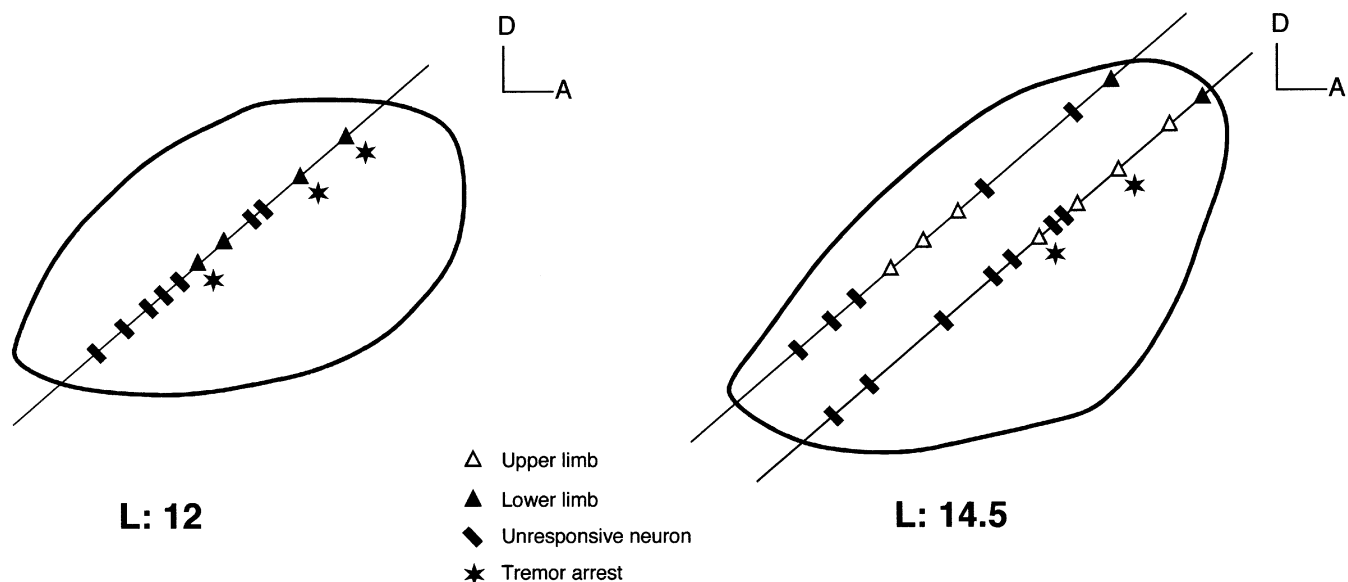


Fig. 2 Somatotopic arrangement of STN neurones responding to passive or active movements in a patient with Parkinson's disease. Two parasagittal planes (atlas of Schaltenbrand and Wahren, 1977) are represented at laterality 12 and 14.5 mm with respect to the AC-PC line. In this patient, the representation of the leg was clearly more medial with respect to the arm. D = dorsal; A = anterior. *Microstimulation in the indicated points selectively stopped tremor of the leg or the arm.

tremor were performed simultaneously. The signals were analysed on the basis of linear spectral methods (Jenkins and Watts, 1968; Lenz *et al.*, 1988). The autopower spectrum was derived after 4 s analysis of the neuronal and EMG signals independently. It provided the intensity of the signal as a function of frequency. Calculation of the spectral cross-power determined the extent to which power in the two signals (neuronal spike \times EMG) has the same predominant frequency. Phase relationships (as assessed by coherence) were not analysed by this method.

Results

Somatotopic organization of the STN

One hundred and eleven neurones (32%) of 350 recorded neurones responded to active and/or passive movement. Five neurones found to respond to both the upper and lower limb of one side, or to the ipsilateral limbs, were excluded from the analysis. Neurones ($n = 24$, 21%) with multi-joint responses within the same limb were included. The distribution of the 111 neurones with movement-related activity in the dorsoventral and mediolateral planes is summarized in Tables 1 and 2, respectively. In the parasagittal plane, the majority of neurones ($n = 87$, 78.3%) were localized in the dorsal third of the nucleus. No neurone with sensorimotor response was found in the ventral segment of the nucleus. Thus, all neurones with movement-related activity were located in the dorsal two-thirds of the STN (Fig. 2). Within this plane a somatotopic arrangement was noticed. The majority of neurones (90%) responding to movement of the leg were located in the upper dorsal third

of the STN. Arm-related neurones were predominantly in the upper dorsal third, but also in the medial segment, and orofacial-related neurones were evenly distributed throughout the dorsal two-thirds (Table 1). From medial to lateral planes, the proportion of neurones responding to movements of the leg decreased, while those responding to arm movement activation increased (Table 2). Neurones sensitive to orofacial movements were mainly found in the 13 mm plane (Table 2). Overall, about two-thirds of neurones with sensorimotor responses were lateral to the 12 mm plane.

In summary, the sensorimotor region of the STN is located in the dorsolateral two-thirds of the nucleus. The lower limb is located in the upper dorsal third and centromedial portion. The arm is placed in the dorsal two-thirds, and lateral region of the STN. The face is also in the dorsal two-thirds, but predominates in the central portion of the sensorimotor region.

Neuronal activity of the STN

Two hundred of the 350 neurones recorded were isolated for 'off-line' analysis. Subthalamic neurones have a biphasic action potential with an initial negative phase followed by a positive phase, a mean duration of 1–2 ms and 400–500 μ V of amplitude. The mean frequency of discharge was 33.12 ± 16.64 Hz (12.7–117 Hz), the mean of the ISI was 37.3 ms and the mean CV of the ISI was 1.28 ± 0.39 .

Three main patterns of neuronal discharges (Figs 3 and 4) were found: (i) irregularly active neurones ($n = 121$, 60.5%) with periods of variable firing activity (irregular pattern); (ii) tonically active neurones ($n = 48$, 24%) with a high frequency of discharge (tonic pattern); and (iii) oscillatory



Fig. 3 Example of the three types of neuronal discharges in the STN (action potentials digitized for analysis and representation): (A) oscillatory, slow activity; (B) tonic, high frequency pattern; (C) irregular activity with long pauses.

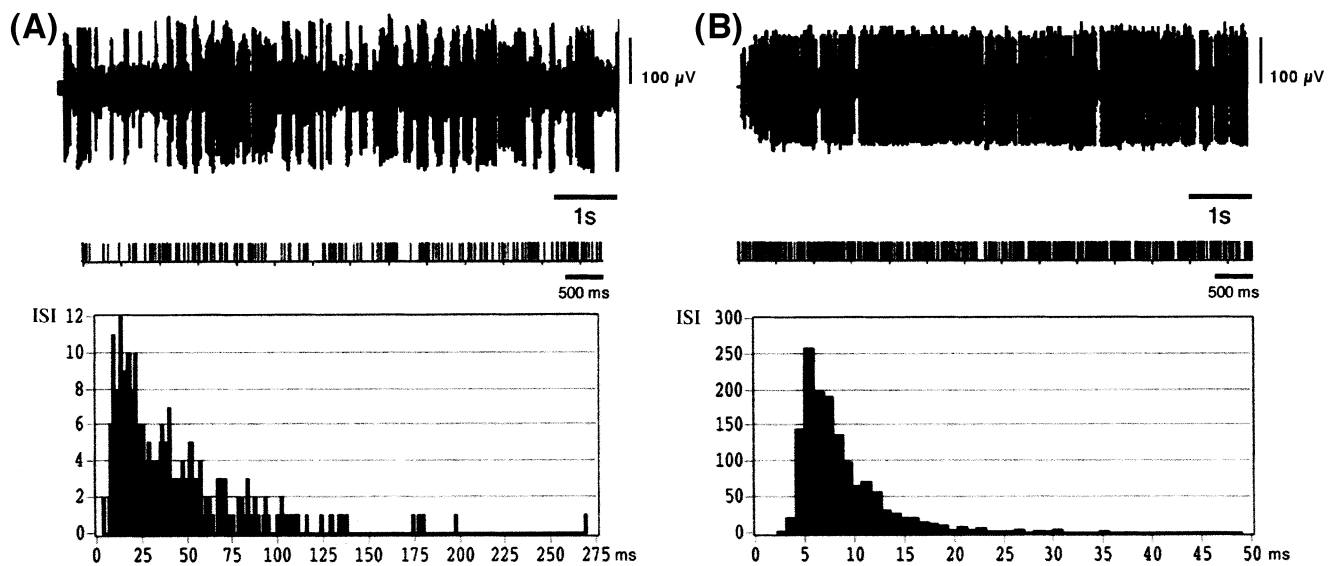


Fig. 4 Spontaneous discharge of a typical irregular (A) and tonic (B) neurone. From top to bottom, the extracellular recorded action potentials, the digitized spike activity and the interspike interval (ISI) histogram. Note the different scale for the ISI due to the small variability in the ISI of the tonically discharging neurone.

neurones ($n = 31$, 15.5%) with rhythmical activity (oscillatory pattern) (Fig. 3). The characteristics of the three types of discharges are summarized in Table 3. There were statistical differences in the mean firing frequency and mean CV of the ISI for the three cell groups (Table 3). Oscillatory, non-tremor-related neurones typically showed long-lasting bursts at a slow frequency (mean 1.8 Hz, range 0.8–2.2 Hz). Neurones with tonic and irregular patterns of discharge had the same proportion of movement-related responses (35 and 34%, respectively). Oscillatory, non-tremor-related neurones had no movement-related activation. Sixteen neurones with oscillatory activity were tremor-related and were analysed separately as described below.

Tremor-related neuronal activity

Thirty-eight neurones with rhythmical activity associated with oscillatory EMG activity in the tibialis anterior or

extensor radialis carpi were recorded (Fig. 5). Most of these tremor-related cells (84%) were responsive to passive stimulation, and were located in the dorsolateral portion of the nucleus.

Microstimulation (100 μ V, 300 Hz, 0.2 ms) at the site where these neurones were recorded, induced tremor arrest with a short latency (<200 ms, data not shown). This effect was limited to specific body segments in accordance with the somatotopic arrangement described above (Fig. 2). The use of a wider pulse duration (>0.5 ms) usually spread the anti-tremor effect to other body regions after a longer delay (1–2 s). Choreatic dyskinesias were occasionally observed during microstimulation when the stimulus was kept on for several seconds at higher current intensity (100 μ A). 'Off-line' analysis of 16 tremor-related neurones was performed (Fig. 6). The autopower spectrum of the neuronal bursting activity and the tremor (EMG activity) had a peak frequency of 6.93 ± 2.22 Hz (4.25–11.5 Hz) and 4.89 ± 0.8 Hz (4.00–

Table 3 Main physiological characteristics of neuronal activity in the subthalamic nucleus

Pattern	Frequency (Hz)	ISI (ms)	CV ISI
Oscillatory ($n = 31$)	24.88 ± 11.99 (19.6–66.6)	49.61 ± 23.5 (1.2–952.2)	$1.91 \pm 0.33^*$ (1.24–2.75)
Tonic ($n = 48$)	50.53 ± 19.98 (24.1–117.1)	$22.38 \pm 7.43^*$ (1.2–402)	$0.93 \pm 0.19^*$ (0.51–1.4)
Irregular ($n = 121$)	28.33 ± 10.25 (12.7–65.4)	39.87 ± 13.8 (1.2–785.8)	$1.26 \pm 0.24^*$ (0.82–2.04)
Total ($n = 200$)	33.12 ± 16.64 (9.6–117.1)	37.28 (3.52–387)	1.28 ± 0.39 (0.51–2.75)

* $P < 0.001$.

6.75 Hz), respectively. The cross correlation showed a peak frequency of 5.11 ± 1.01 Hz (4.25–8.00 Hz) (Fig. 6), thus indicating a significant association between the rhythmic neuronal discharge and tremor activity in the limbs. However, the relationship between firing of an isolated neurone and tremor of the limbs may be complex. For instance, Fig. 5 shows rhythmical bursting activity of a neurone which is phase-related to both the contralateral triceps and biceps of the upper limb and the tibialis anterior of the lower limb (Fig. 5B–F). Examination in more detail revealed that such neuronal activity was actually phase-locked to EMG activity of the upper limb, but not to the tibialis anterior muscle (Fig. 5G–H).

Movement-related neuronal activity in the STN

The neuronal response associated with active movements was studied by simultaneous recording of neuronal activity and EMG activity of the limbs. Five tremor-related neurones, recorded while a voluntary movement was performed, were available for analysis. Voluntary activation of a particular limb segment arrested the tremor. This was associated with a change in the discharges of the recorded neurone, which fired at a slower rate and in synchrony with the voluntary movement (Fig. 7). On occasions, freezing of the voluntary movement ensued and tremor reappeared, changing the neuronal activity back to the typical 4–5 Hz tremor-related activity. The cross-correlation analysis of two such neurones showed a peak frequency of 4.63 and 4.88 Hz for tremor-related activity, and of 1.5 and 1.38 Hz during voluntary movement. Whether neuronal discharges in the STN preceded or followed EMG activity of the limbs could not be precisely established under the present conditions.

Neuronal activity of the SNpr

Neuronal activity of the SNpr was recorded 0.5–3 mm below the STN. Eighty neurones were recorded 'on-line'. The action potentials during the recording were biphasic, with high frequency and brief duration (1–2 ms), and a predominant tonic pattern of discharge. Of the 80 neurones recorded, 27 were adequately isolated for 'off-line' analysis. These neurones showed a tonic pattern of discharge characterized by a mean firing rate of 71.59 ± 28.33 Hz (35–122 Hz) with a mean ISI of 16.44 ± 7.01 ms and a mean CV of the ISI of 0.85 ± 0.29 (Fig. 8). In only three neurones (11%) was

there a response to sensorimotor stimulation. Comparing SNpr neurones with the group of STN neurones with a tonic firing pattern, the SNpr had a significantly ($P < 0.001$) higher firing discharge rate; however, there was no difference in the CV of the ISI, indicating that both neuronal groups discharged with a similar pattern.

Discussion

Somatotopic arrangement

The present study describes the somatotopic arrangement of the STN in Parkinson's disease and the characteristics of neuronal discharge in the parkinsonian state. We found that neurones responding to passive and active movements were largely restricted to the dorsolateral region of the STN. The proportion (32%) of movement-related neurones in our patients was within the range found in the STN of normal monkeys for active and passive movements (DeLong *et al.*, 1985; Wichmann *et al.*, 1994b). A similar proportion of sensorimotor responses has been reported for the GPM in both MPTP monkeys (Filion *et al.*, 1988) and Parkinson's disease patients (Taha *et al.*, 1996; Vitek *et al.*, 1998; Guridi *et al.*, 1999). Within the dorsolateral region of the STN, the arm representation is mainly (77%) in the lateral planes (>12 mm). The leg is more medially distributed as 51% of neurones were found medial to the 12 mm plane. Neurones corresponding to the face and oromandibular muscles were also distributed in the lateral planes (87.5%) (>12 mm), but were found predominately in the middle (~13 mm) portion of the STN, and were ventral to the arm and leg region. Overall, the somatotopic organization of the STN in Parkinson's disease appears to be similar to that described in the normal monkey (DeLong *et al.*, 1985; Wichmann *et al.*, 1994b; Nambu *et al.*, 1996). In the GPM of MPTP monkeys, the sensorimotor fields are augmented (Filion *et al.*, 1988). Therefore, it is possible that the somatotopic representation of the STN in Parkinson's disease patients could be distorted. Recent studies in Parkinson's disease patients, however, have shown a somatotopic organization for the GPM (Vitek *et al.*, 1998; Guridi *et al.*, 1999) similar to the one described here for the STN. This suggests that in humans, as in monkeys, the motor circuit maintains a general anatomical organization throughout the basal ganglia (DeLong and Georgopoulos, 1981). Nevertheless, a certain degree of variability for our findings is not surprising due to

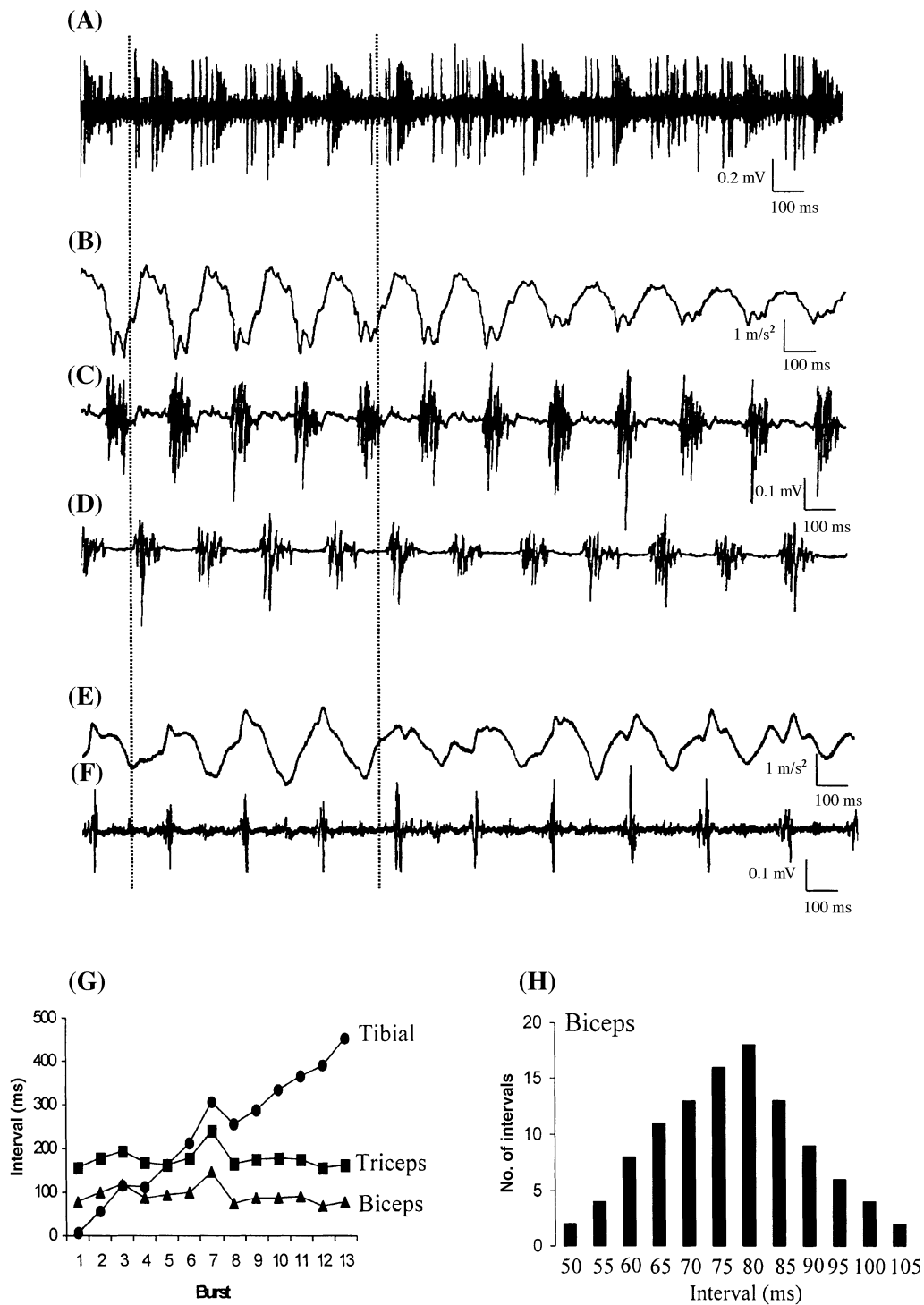


Fig. 5 Rhythmical neuronal discharges in the dorsolateral STN (A) during simultaneous recording of tremor in the upper (B, accelerometer; C and D, EMG activity in the biceps and triceps muscles of the arm) and lower (E, accelerometer; F, EMG of the tibialis anterior muscle) limbs. The onset (vertical dotted lines) of each burst of neuronal activity is time-locked to the EMG discharges (intervals) in biceps and triceps (G, H) but progressively loses its relationship with the tibialis anterior muscle of the leg (G). The initial discharges of each burst (as indicated by the dotted lines in A–F) were taken as the onset point for the analysis.

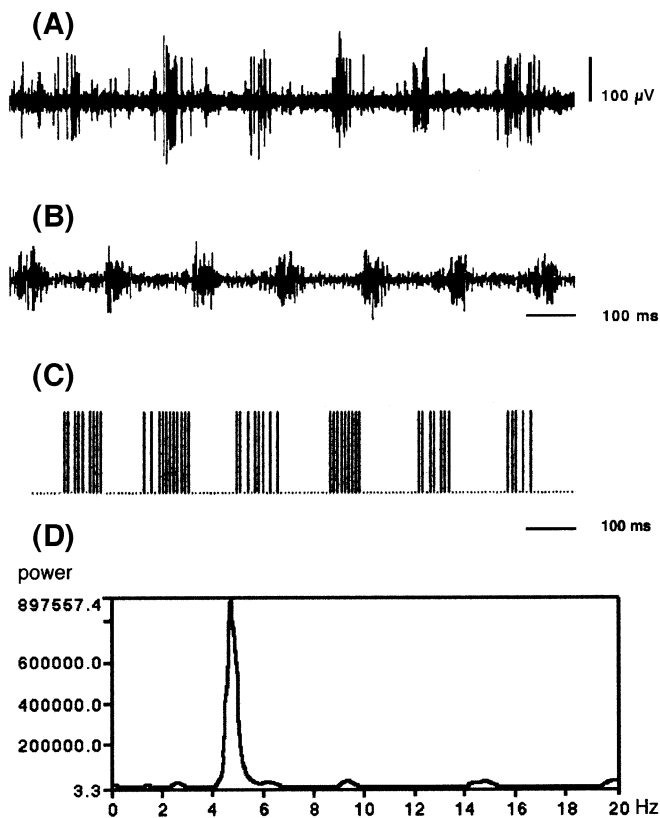


Fig. 6 Analysis of tremor and STN activity. (A) Rhythmic neuronal discharges and (B) simultaneous electromyographic activity in the wrist extensor muscles. The digitized action potentials (C) of record shown in A were used for cross-power analysis of neuronal and tremor-related activity in the forearm. A well-defined peak at 5.1 Hz is shown (D).

a number of methodological issues and confounding factors. Thus, the somatotopic organization of the STN in Parkinson's disease patients has been undertaken analysing the neuronal activity in a fairly high number of patients, and choosing only a few adequately isolated neurones per subject. Both time constriction and variable patients' cooperation limit the analysis of movement-related neurones in the operating theatre. This situation does not allow us to reproduce the experimental conditions in monkeys. In addition, the methodology applied to define the planes, i.e. MRI imaging, has an intrinsic variability. Taking all these variables into consideration, the results are relatively consistent and provide a good indication of the somatotopic arrangement of the sensorimotor region of the STN in Parkinson's disease.

Neurones with sensorimotor responses in the STN of parkinsonian patients are most likely to represent those receiving afferent principally from the primary motor cortex, which is known to project to the dorsolateral STN in the monkey (Nambu *et al.*, 1996). Projections from the premotor area and supplementary motor area are also somatotopically organized, but synapse mainly in the dorsomedial region of the STN (Nambu *et al.*, 1997), and probably require more complex motor tasks to be activated. Taking the available

experimental data, together with our findings, it is quite likely that the dorsolateral STN is the region of the nucleus most directly related to the development of the cardinal motor features of Parkinson's disease. Neurones located in the ventral and medial region of the STN have no sensorimotor responses, and are reciprocally connected with the associative and limbic cortical regions (Parent and Hazrati, 1995; Maurice *et al.*, 1998). Accordingly, the dorsolateral STN is the surgical target in Parkinson's disease. Lesions of the STN in the rat have been associated with behavioural deficits such as premature and perseverative responses, and deficits in discriminative accuracy during attentional tasks (Baunez *et al.*, 1995; Baunez and Robbins, 1997; Henderson *et al.*, 1999; Phillips and Brown, 2000). DBS of STN in Parkinson's disease patients improves executive motor functions, but aggravates conditional associative learning (Jahanshahi *et al.*, 2000; Saint-Cyr *et al.*, 2000). In principle, blocking (by lesioning or DBS procedures) abnormal neuronal activity in the dorsolateral region of the STN while sparing the medioventral portion should convey the best anti-parkinsonian effect with minimal side-effects. The somatotopic arrangement of the STN in Parkinson's disease unravelled in the present study is not only of theoretical importance, but may also have practical interest for either DBS (Benabid *et al.*, 2000) or subthalamotomy (McCarter *et al.*, 2000; Alvarez *et al.*, 2001) in patients with Parkinson's disease.

Neuronal activity

We have identified three types of neuronal activity (tonic, irregular and oscillatory) on neuronal firing patterns in the STN of Parkinson's disease. The most frequent (60.5%) type consisted of irregular discharges with silent periods or pauses of 50–200 ms, and a mean firing rate of 28.33 Hz (12.7–65.4 Hz). A second, less frequent, type of discharge (24%) had a tonic pattern with a mean firing rate of 50.5 Hz (24–117 Hz). These two types of discharge were statistically differentiated on the basis of their mean firing rate, ISI-histogram and CV of the ISI. However, in the monkey, the cellularity of the STN is homogeneous (Parent and Hazrati, 1995) and it is possible that the differences encountered here may reflect different states of excitability of a similar neuronal population. As a consequence, the difference between neurones with a tonic or irregular firing pattern may represent sampling bias at the time of recording (e.g. see Fig. 3). In keeping with this interpretation is that neurones with both types of firing pattern were equally activated by movement. A small proportion of neurones in the STN discharged rhythmically with long-lasting (200–400 ms) bursts at a very slow rate (Fig. 3A). This activity was found mainly in the ventral third of the STN, and was not sensitive to movement. Such slow rhythmic neuronal activity is clearly different from the tremor-related discharges recorded in the STN. Thus, tremor-related cells had a higher frequency of burst discharges (6.9 Hz for tremor-related cells versus 1.8 Hz for rhythmical non-tremor-related cells), were sensitive to

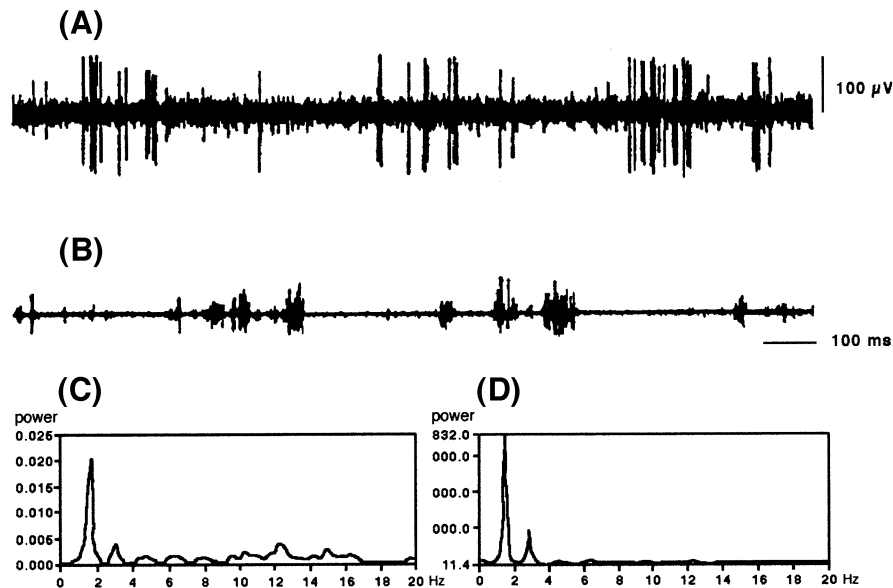


Fig. 7 Neuronal discharges in the STN (A) and EMG activity (B) of the wrist extensor muscles during repetitive tapping movements. Autopower of the movement (C) and cross-powered analysis (D) between neuronal and EMG activity showed a peak at 1.5 Hz and 1.4 Hz. The EMG shows the typical multiple burst cycles associated with bradykinesia and, interestingly, a similar pattern is seen in the neuronal activity. The repetitive movement performed in this instance precluded analysis of the relative timing of neuronal to EMG activity.

movement of the limbs and face and were mainly found in the dorsolateral region of the STN in register with the somatotopic organization described above. Interestingly, the frequency of discharge of the cells with slow bursts is similar to the ones recorded in the globus pallidus lateralis (GPI) of monkeys (DeLong *et al.*, 1985) and parkinsonian patients (Lozano 1996; Vitek *et al.*, 1998). Slow oscillatory discharges unlocked with tremor activity in the limbs are also present in Parkinson's disease patients in the ventrolateral nuclei of the thalamus (Magnin *et al.*, 2000). The precise significance of the non-tremor-related bursting activity in the basal ganglia remains to be defined. The mean firing frequency of neuronal activity in the STN of our patients was 33.12 ± 16.64 Hz (12.7–117 Hz). This is similar to the one reported by Hutchison and colleagues (37 ± 17 Hz) in Parkinson's disease patients (Hutchison *et al.*, 1998), but not quite in agreement with the recent results of Magariños-Ascone *et al.* (2000). The latter authors found a higher firing rate of ~60–70 Hz, and essentially a neuronal discharge pattern similar to the one we described above. It is therefore possible that methodological differences in the isolation, sorting and analysis of the spikes may explain these differences.

Tremor- and movement-related activity

The origin of rest tremor in Parkinson's disease is not well understood. Neuronal discharges phase-locked to tremor have been known to occur in the thalamus since the pioneering work of Albe-Fessard, and subsequently have been analysed in more detail (Albe-Fessard, 1962; Ohye and Narabayashi,

1979; Lenz *et al.*, 1994). More recently, rhythmical neuronal firing at the tremor frequency has also been documented in the GPM of patients with Parkinson's disease undergoing pallidotomy (Vitek *et al.*, 1998; Guridi *et al.*, 1999; Lemstra *et al.*, 1999). The participation of the STN in the origin of tremor was anticipated by the study of Bergman and colleagues in MPTP monkeys where tremor-related discharges were found (Bergman *et al.*, 1994), and by the drastic antitremoric effect of lesions or high frequency stimulation of the STN in parkinsonian monkeys (Benazzouz *et al.*, 1993; Wichmann *et al.*, 1994a; Guridi *et al.*, 1996). More recently, a significant antitremor effect in Parkinson's disease patients treated with DBS of the STN has been reported (Krack *et al.*, 1997; Limousin *et al.*, 1998; Rodriguez *et al.*, 1998; Benabid *et al.*, 2000). In the previously published physiological studies of the STN in Parkinson's disease, 'tremor cells' were described (Hutchison *et al.*, 1998; Magariños-Ascone *et al.*, 2000; Levy *et al.*, 2000). Our findings provide further evidence as to the role and characteristics of tremor-related activity in the STN of Parkinson's disease patients. We also found tremor-related cells in the STN with a predominant frequency for both neural firing and tremor in the limbs of 5.1 Hz. Microstimulation induced immediate tremor arrest when the microelectrode was in a STN zone where 'tremor-related' neuronal activity was being recorded, and such an effect occurred in a somatotopically dependent fashion (Fig. 2). These observations indicate that the STN is part of the neuronal chain involved in the origin of parkinsonian tremor, but do not allow us to define whether neuronal STN activity

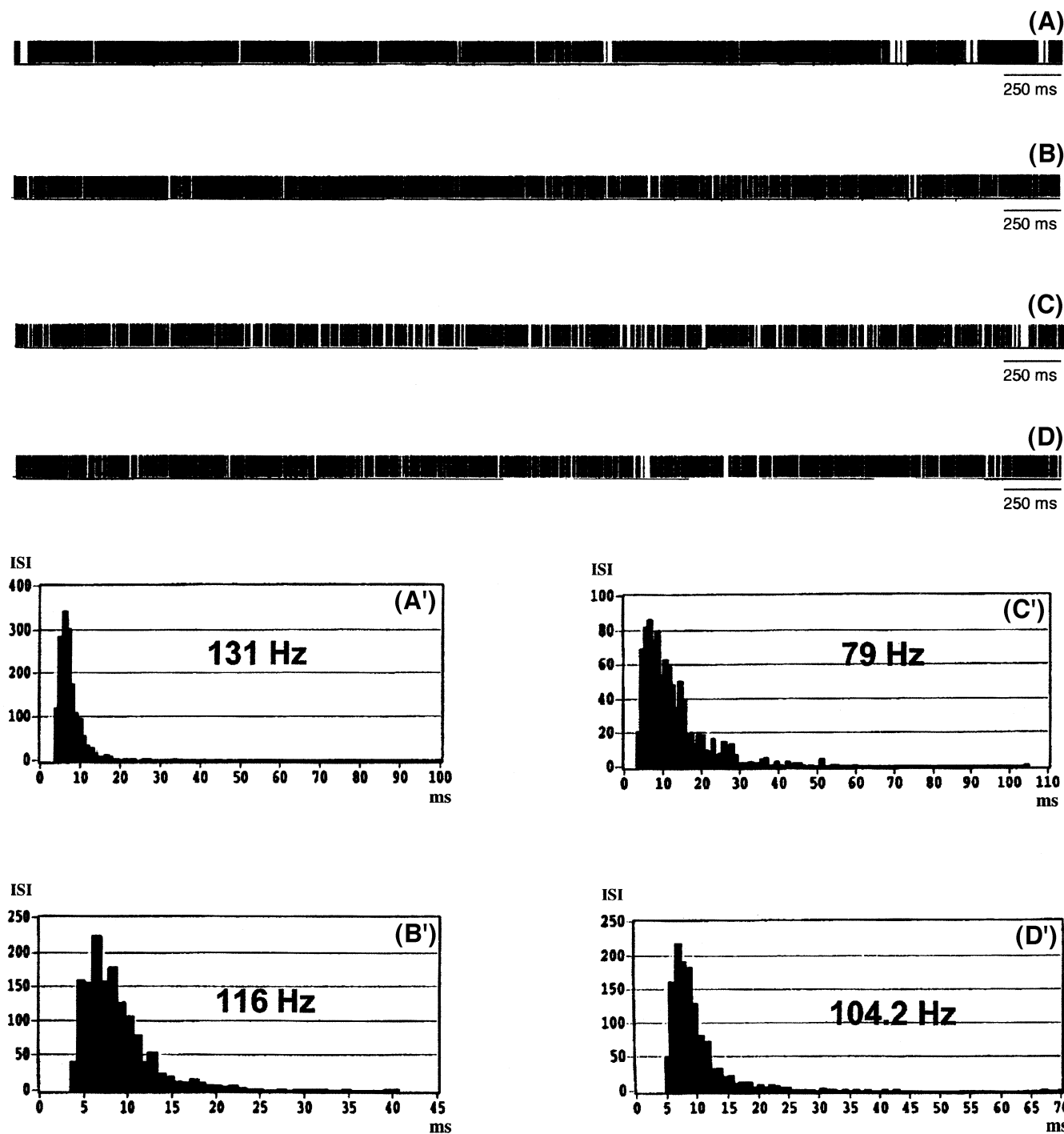


Fig. 8 Examples of the digitized spikes of four neurones from the substantia nigra pars reticulata and the corresponding ISI histogram. A tonic pattern with a high firing rate is clearly present.

antedates or follows EMG tremor discharges in the limbs. Relevant to this latter point are a number of qualitative observations in the present study. Thus, most neurones discharging in phase with tremor were also sensitive to passive and active movement of the limbs, and the location of ‘tremor-related’ cells coincided with the somatotopic arrangement of the STN. Indeed, the occurrence of time and

phase-locked neuronal activity and EMG tremor discharge seems to be specific and independent for different body segments (Fig. 5), an observation also made for the GPM by Hurtado and colleagues (Hurtado *et al.*, 1999). Similarly, analysis of tremor in different muscles of patients with Parkinson’s disease and essential tremor revealed lack of coherence between muscles of the upper and lower limbs

(Raethjen *et al.*, 2000). Altogether, these findings support the idea that tremor in Parkinson's disease is mediated by multiple oscillatory loops which utilize the somatotopic and parallel arrangement of the motor circuit through the basal ganglia (Alexander *et al.*, 1986; DeLong, 1990; Middleton and Strick, 1997). On the other hand, in Parkinson's disease patients with tremor, Levy and colleagues found synchronization at a high firing rate (>10 Hz) while recording pairs of neurones sited >600 μm apart (Levy *et al.*, 2000). However, coherence among tremor cells in the STN of the same patient was not a universal finding (Levy *et al.*, 2000), in keeping with the above suggestion of parallel 'tremor circuits'.

We observed that during the performance of a voluntary movement, tremor stopped in the recruited body segment and the oscillatory, tremor-related neuronal activity in the STN gave way to slower burst firing, synchronous with the voluntary movement (Fig. 7). A similar observation has been made previously by Magariños-Ascona *et al.* (2000). Recording EEG cortical activity and STN local field potentials (from electrodes implanted for DBS) showed significant coherence at the beta and gamma frequency bands during movement (Marsden *et al.*, 2001). These observations are in keeping with the well-described corticosubthalamic motor projection (Nambu *et al.*, 1996), and suggest that the STN neurones involved in parkinsonian tremor are the same as the ones activated during the performance of a voluntary movement. A similar suggestion has been made by Duffau and colleagues on the basis of activation studies with PET (Duffau *et al.*, 1996). While we cannot prove that parkinsonian tremor is generated in the STN itself, the STN certainly plays a fundamental part in the distributive network involved in the origin of tremor. It has been shown recently (Plentz and Kitai, 1999) that the reciprocal inhibitory–excitatory connections tightly linking the GPi and the STN (Ryan and Clark, 1991, 1992) may generate self-perpetuating oscillations. Under certain conditions, rhythmical cortical activity is time-locked with neuronal activity in the STN and globus pallidus (Bevan and Wilson, 1999; Magill *et al.*, 2000). Recent studies indicate that the biophysical characteristics of the membrane in subthalamic neurones are adequate to form spontaneous, high frequency discharges (Beurrier *et al.*, 1999; Bevan and Wilson, 1999). It is possible that, in the parkinsonian state, glutamatergic afferent activity to the subthalamic nucleus is also augmented (Orieux *et al.*, 2000), which would increase STN excitability and the tendency to generate rhythmical discharges. It is tempting to speculate, therefore, that dopaminergic depletion in Parkinson's disease increases neuronal synchronization in the motor circuit (Bergman *et al.*, 1998) leading to oscillatory activity in basal ganglia nuclei such as the GPi, STN and GPM, as well as in the thalamus and motor cortex. This would explain why interrupting neuronal activity in any one of these structures stops tremor in Parkinson's disease.

Substantia nigra pars reticulata

Neuronal activity corresponding to the SNpr was detected immediately ventral to the STN in a high number of recording

tracks. In the normal monkey, the SNpr has a mean firing rate of 60 Hz and maintained the general somatotopic organization of the basal ganglia (DeLong *et al.*, 1983). In the MPTP monkey, neuronal firing and metabolic markers (GADmRNA and COMRNA) in the SNpr are elevated above normal (Vila *et al.*, 1996, 1997; Wichmann *et al.*, 1999). In Parkinson's disease, Hutchison and colleagues reported a mean firing rate of 71 ± 23 Hz ($n = 56$), and the pattern of discharge was tonic (Hutchison *et al.*, 1998). Our results coincide almost exactly with Hutchison and colleagues' data. We found a mean firing rate of 71 ± 59 Hz. The CV of the ISI was 0.85 according with the marked tonic discharge pattern of SNpr neurones, and in keeping with findings in MPTP monkeys (Wichmann *et al.*, 1999). Sensorimotor responses were infrequent in the SNpr compared with the findings in the STN and GPM of Parkinson's disease patients. Tremor-related cells were never recorded.

In summary, the data presented here lead us to suggest that the electrophysiological activity of the STN in Parkinson's disease is similar to that described in MPTP monkeys, which is increased over that in control animals. Since there are no control data in humans, we cannot be completely certain about the level of activity of the STN in Parkinson's disease. The demonstrated clinical efficacy of surgery of the STN in Parkinson's disease (Limousin *et al.*, 1998; Alvarez *et al.*, 2001), and the accompanying restoration of movement-related cortical activity shown by PET (Limousin *et al.*, 1997), support the concept of hyperactivity of the STN in Parkinson's disease. The somatotopic arrangement of the STN described here may prove useful in achieving better surgical results with fewer side-effects.

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