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ANALYSIS OF EVOKED ACTIVITY PATTERNS OF HUMAN THALAMIC VENTROLATERAL NEURONS DURING VERBALLY ORDERED VOLUNTARY MOVEMENTS

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Abstract––In the human thalamic ventralis lateralis nucleus the responses of 184 single units to verbally ordered voluntary movements and some somatosensory stimulations were studied by microelectrode recording technique during 38 stereotactic operations on parkinsonian patients. The tests were carried out on the same previously examined population of neurons classified into two groups, named A- and B-types according to the functional criteria of their intrinsic structure of spontaneous activity patterns. The evaluation of the responses of these units during functionally different phases of a voluntary movement (preparation, initiation, execution, after-effect) by means of the principal component analysis and correlation techniques confirmed the functional differences between A- and B-types of neurons and their polyvalent convergent nature. Four main conclusions emerge from the studies. (1) The differences of the patterns of A- and B-unit responses during the triggering and the execution phases of a voluntary movement indicate the functionally different role of these two cell types in the mechanisms of motor signal transmission. (2) The universal non-specific form of anticipatory A- and B-unit responses during the movement preparation and initiation of various kinds of voluntary movements reflect the integrative ''triggering'' processes connected with the processing and programming of some generalized parameters of a motor signal and not with the performance of a certain forthcoming motor act. (3) The expressed intensity of these ''triggered'' non-specific processes in the anterior parts of the ventralis lateralis nucleus indicates their relation not only to the motor but to the cognitive attentional functions forming a verbally ordered voluntary movement. (4) The appearance of the transient cross-correlations between the activities of adjacent A- and B-cells and also the synchronization of their 5 ± 1 Hz frequency during and/or after motor test performances point to the contribution of these two populations to central mechanisms of the voluntary movement and the parkinsonian tremor.

The functional role of two A- and B-cell types is discussed with references to the central mechanisms of verbally ordered voluntary movements and the parkinsonian tremor. © 1998 IBRO. Published by Elsevier Science Ltd.

Key words: human thalamic ventralis lateralis nucleus, microrecordings, unit evoked activity, verbally ordered voluntary movement, parkinsonian tremor, principal component analysis.

The study of motor control mechanisms at the single cell level is important for understanding the functional organization of motor functions and their disturbances. In the light of the recent experimental investigations the motor control is represented by parallel segregated multiple distributed systems including large populations of neurons in the forebrain and subcortical structures co-ordinating temporally and spatially during movement performance.[6,7,24,29,35,50,57,59] The nucleus ventralis lateralis thalami (VL), because of its nodal position in the re-entrant loops involving the cerebral cortex with cerebellum and basal ganglia, is one of the important subcortical motor centres participating in information processing during movements.[8,19–21,30,36,41,46,47,50,78] However, the neuronal organization and the role of the VL in the control of voluntary movements is still an open question.

Taking into account the human higher nervous specificity to perform a verbally ordered voluntary movement, the microelectrode recordings as a mean of localizing target during stereotactic operations on parkinsonian patients provide a perspective approach to study the motor functions. The pioneer papers of Albe-Fessard and her associates[3–5] and subsequent investigators using microrecordings have described in the thalamic ventral nuclear group, especially in the nucleus ventralis intermedius thalami (Vim) and surrounding structures of

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parkinsonian patients, the alterations of cell activity related to active movements[15,28,33,44,54,61–64,80,82] and also to some somatosensory stimulations.[3–5,33,42,45,52,54,55,62,63,80] We have found in some non-specific and associative nuclei of the human thalamus and in the striatum a special class of convergent neurons, which selectively responded to the verbal commands causing a subject to start voluntary movements.[61–63,65–67] In the companion paper[69] we have described the intrinsic structure of spontaneous activity (SA) of VL units and shown that it allows the classification into two groups, named A- and B-types.

The aim of the present study was: (i) to make a quantitative analysis of the evoked activity (EA) patterns on the same populations of VL neurons related to both the performance of verbally ordered voluntary movements and some somatosensory stimulations, and (ii) to elucidate the role of the human VL in the information processing during functionally different stages (preparation, initiation and execution) of an intended active movement.

EXPERIMENTAL PROCEDURES

The present data are based upon single unit analysis of the EA patterns of 490 cells recorded during 38 stereotactic operations in the VL of parkinsonian patients (surgeons—A. Kadin, N. Vasin, V. Shabalov, N. Grochovsky, A. Shtock). Of them, the responses of 184 neurons analysed by computer techniques in relation to both the verbally ordered voluntary movements and some somatosensory stimulations. The SA of the same neuronal population has been examined elsewhere.[69] The studies on patients were accomplished following the principles of the Declaration of Helsinki. All surgical and physiological procedures were used in order to improve the treatment only after careful explanations to the patients, provided that their written consents were received.

Microrecordings and methodology of the verbally ordered movement cell testing

Unitary extracellular activity was recorded with tungsten microelectrodes (1–5 μm at the tip, resistance from 1–5 MΩ). The location of the VL was determined by ventricular X-ray screening or computer tomography scan and based on the human brain atlas by Schaltenbrand and Bailey.[72]

The following wide range of active motor tests was used: clenching–unclenching the fist, lifting–lowering the upper and lower extremities, flexion–extension of the leg, etc. According to the elaborated methodology of verbally ordered functional cell testing[61–63,67] these tests were performed in response to verbal commands, such as: "Clench your hand!", "Unclench!", etc. The performance of above motor tests allowed to estimate the changes in the EA patterns of units related to both the functionally different phases of voluntary motor act (preparation, initiation, execution, after-effect) and the different parameters of limb movement such as force amplitude (or capacity) of appropriate motor execution. The EA pattern of units was also examined in relation to some somatosensory stimulations including joint passive movements (flexion–extension of the wrist, elbow, leg, etc.), light touch, shutting–opening the eyes. As a rule, three to 10 tests were analysed in each point: before (3–5 s), during (5–10 s) and after (3–5 s) the test performance. Changes in neuronal and electromyogram

(EMG) activities were analysed with respect to the following functionally different phases of the verbally ordered voluntary movement: (i) before the stimulus presentation; (ii) the preparation phase from a moment of the imperative accent of the verbal command presentation till the beginning of initial EMG changes; (iii) the phase of the movement initiation and execution indicated by the EMG changes; (iv) the final phase of the movement termination and its after-effect.

As a physiological measure of various voluntary movements, the EMG (bandwidth 15–500 Hz) of the tested extremities was recorded contra- and ipsilaterally to the explored thalamus from the following muscles: finger flexors and extensors, biceps or deltoid, quadriceps or gastrocnemius, trapezius. Together with unit and EMG activities, the surface electroencephalogram, the electrooculogram, the mechanogram and the phonogram of verbal and sound stimuli were recorded simultaneously on photoregistrator, tape recorder, electroencephalograph and monitored through oscilloscope and loudspeaker.

The techniques of data analysis

Spikes from two to three simultaneously recorded adjacent cells were separated with an amplitude discrimination of spikes and the cluster and factor analyses of their forms. The EA of units was analysed with computer techniques. The following functions were estimated: firing rate frequency, peristimulus rasters of spikes or bursts, peristimulus firing rate histograms (PSHs) of units with averaged EMG responses and phonogram signals; autocorrelation and spectral power functions (bin=20–200 ms). The interneuronal connections and relationships between neuronal and EMG changes were estimated with the correlation and the coherence functions (bin=20–200 ms). The following parameters of the EA patterns of units during functionally different stages of the motor test performance were evaluated: sign of reactions, intensity (ratio of the definite phase firing rate frequency of responses to the rest), latency of responses from the imperative accent of the command presentation and/or from the initial EMG changes, duration of neuronal and EMG responses.

Taking into account the dynamics and variability of unit responses of behaving human brain, the method of principal component analysis (PCA)[17] was used to investigate the structure of EA patterns of neurons during the functionally different stages of a voluntary movement (preparation, initiation, execution). This method (see also techniques in Ref. 67) allows to decompose the EA pattern of units into a set of independent components and to compare these constituents in relation to both the temporal proceeding and the dynamics of reactions during functionally different phases of the test realization. Moreover, this analysis permits to avoid averaging that is inevitable to the PSH construction. As a rule the PCA was based on six to 12 trials. In general, two to three principal components (PCs) were extracted so that the sum of their eigenvalues was not less than 0.8. In addition to examine the relationship between adjacent units we used peristimulus cross-correlation (PSC) matrices.[17,22] These were displayed on a two-dimensional plane. Significant positive cross-correlations (95%) between adjacent pairs of units were marked by black dots. The beginning for construction of the cross-correlation matrices and the PCA was a moment of the imperative accent of the verbal command presentation and/or a moment of the onset of the movement realization. On the axes the reaction latency and the time of appearance of significant correlation coefficient (larger than 0.6–0.8) were marked for each unit. The technique of PCA with PSC matrices has been previously applied to the study EA patterns of neurons of the human thalamic reticularis nucleus (RT).[67] The statistical analysis was applied to reveal correlations of EA patterns of units

with their spatial location and also with the form of parkinsonian pathology.

The details of our surgical procedure, microelectrode recording and computer processing techniques were described previously.[62,63,67–69]

RESULTS

Characteristics of the evoked activity patterns of ventrolateral neurons

The A-type units (unitary irregular 2–40/s *spontaneous discharges,* 142 *out of* 184 *studied,* 77%*)*. The majority of responsive A-units (128 out of 142, 90%) showed close connections with the preparation and the performance of motor acts more pronounced on the contralateral side. More than a half of all A-units (73 out of 128, 57%) during the performance of various voluntary motor tests reacted by a tonic (duration 1–4 s) activation with multiphasic, mainly three-phasic fluctuations of spike frequency related to the following functionally different phases of movement: the triggering phase (preparation and initiation), the movement execution and its after-effect. Figures 1, 2A and 3A present examples of the main discharge patterns of unit responses in relation to these phases.

As seen in Figs 1, 2A and 3A, a tonic activation of spike discharges began about 400–700 ms before the onset of the EMG changes and lasted throughout the entire period of the muscle contraction. During the first motor task performance the duration of activation was about 700 ms. During the performance of successive repetitive movements it decreased from 700 to 400 ms and was accompanied by reduction in a latency of EMG changes without any modifications in their amplitude. This anticipatory activation, more pronounced in the anterior VL (nucleus ventrooralis anterior, Voa), correlated in time with the triggering phase of motor test performances (the period of preparation and movement initiation) (47 out of 128, 37%). This was demonstrated by reproducible distribution of spike discharges during repeated motor tests (see raster diagram in Fig. 1). A-units located in zones adjacent to the RT and the zona incerta (Zi) nuclei had been activated earlier, preceding the EMG changes of 0.7–1.0 s with a latency of 200–300 ms after the imperative accent of the verbal command presentation (9 out of 128, 7%). In the posterior VL (nucleus ventrooralis posterior, Vop) the expression of anticipatory activations during the triggering phase of movements was far less than in the anterior areas (26 out of 128, 20%), the intensity and the duration of firing rate discharges during the movement execution was much greater (43 out of 128, 34%). During the final phase—the termination of voluntary movements, when the decrease of muscle contraction was observed, all A-units responded phasically by a decrease or an inhibition of spike discharges. Just after the movement completion an increase in

firing rate of discharges of 0.5–1 s duration was observed as a rebound effect (38 out of 128, 30%) (Figs 1, 2, 3A, 6). It should be noted that during the apex of muscle contraction and/or its after-effect a transient transformation of the unitary non-rhythmic discharge pattern into a 5 ± 1 Hz rhythmic one was also observed and mostly in the posterior VL (40 out of 128, 36%) (Fig. 7). The analysis of parameters of the EA pattern of neurons occurring during the triggering anticipatory activation and during the late activation revealed some interesting differences: a tendency to decrease in duration for the anticipatory changes and a tendency to increase in intensity for the late activation. This tendency was observed in rigid and akinetic patients and mainly in the anterior VL (27 out of 128, 21%).

It is important to note that the performance of a wide range of motor tests (movement of upper and lower extremities of contra- and ipsilateral side) requiring differences in their force amplitude and muscle activities was accompanied by a relatively constant activatory configuration of the EA pattern of A-neurons. More expressed uniform activation was observed during the triggering phase of various voluntary movements and mainly in the anterior VL (Figs 1, 2, 6A). In the posterior VL the execution phase of different-ordered movements was characterized by the more modified configuration of fluctuations in firing rate of discharges correlating with the force amplitude and capacity of muscle contraction.

The analysis of the location of responsive A-units revealed that this type of neuron is spread relatively homogeneously in dorsoventral directions of the VL. The specificity of responses in relation to the particular motor test performances of appropriate limbs increased in the caudal direction. The majority of cells located in the posterior VL (52 out of 128, 40%) showed more specific characteristics. Units located at the boundary between Vop and Vim nuclei (10 out of 128, 8%) were activated only during the execution of particular movements of the contralateral side and showed a tendency to a somatotopic specificity (Fig. 2).

The EA patterns of VL neurons were examined not only during a wide range of voluntary movements but also during some somatosensory stimulations (passive movements, opening and closing the eyes, etc.). As illustrated in Fig. 3, the A-units (20 out of 22 observed, 91%) located mainly in the anterior VL were activated by stimuli provoking an arousal-like reactions. The essential feature of these reactions was their quick disappearance after two to four successive repetitions of stimulations. Unlike the arousal-like reactions, the responses to movement performances in the VL were stable. Moreover, the tendency to an increase of discharge frequency during the triggering phase and, especially, during the rebound late activation was observed after repetitive motor test performances in the majority of responsive units (57%).
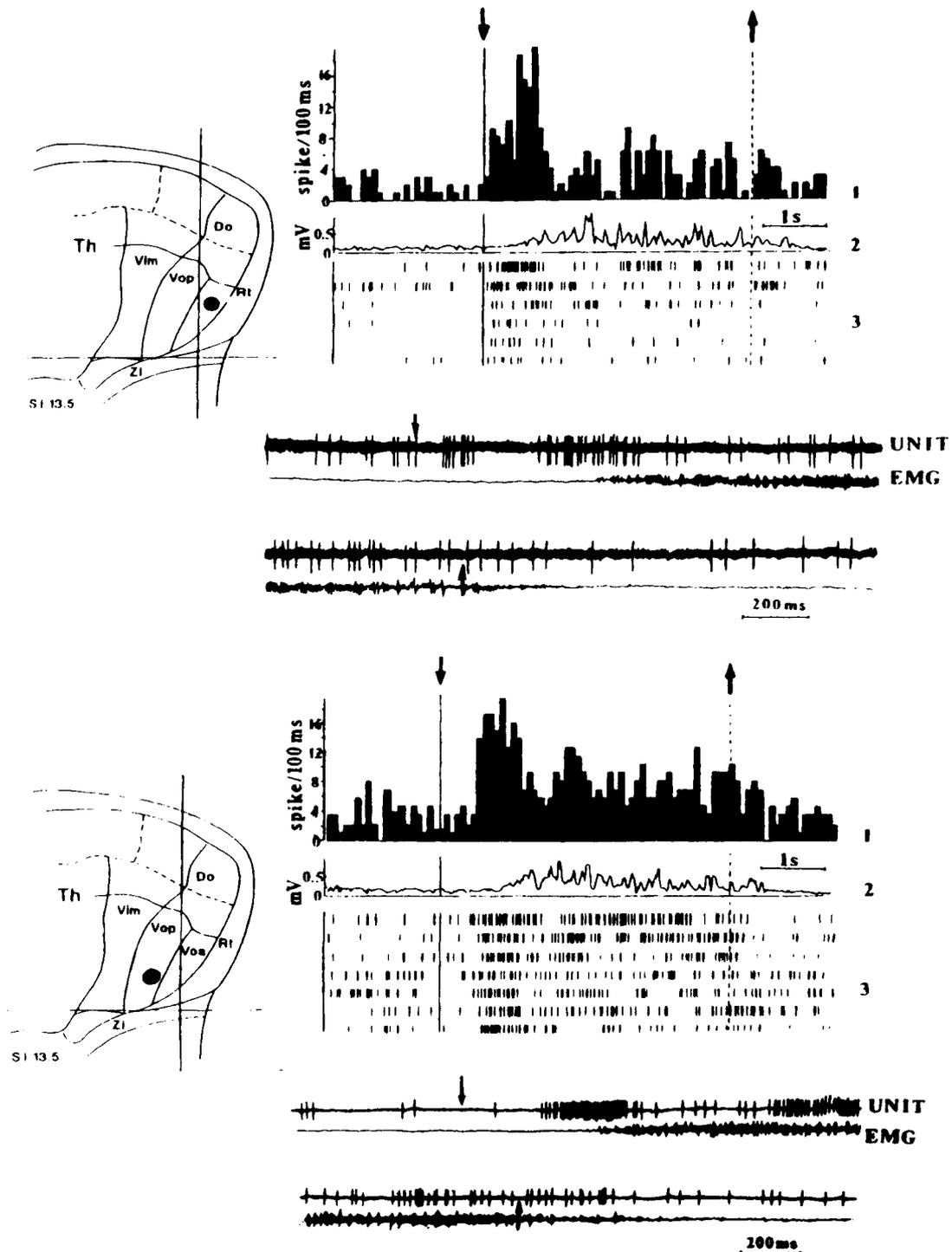
Fig. 1. Characteristics of EA patterns of A-type units in the anterior (above) and the posterior (below) parts of the human VL during the verbally ordered voluntary movement performance (finger flexion–extension). At left: scheme of the human thalamus in a sagittal plane according to the atlas of Schaltenbrand and Bailey[70] and the position of investigated zone (black dot). At right: peristimulus firing rate histograms (1), averaged EMG of contralateral finger flexors (2), rasters (3) and corresponding fragments of extracellular spiking and EMG activities. The arrows mark the time of imperative accents of verbal commands "Clench your fist!" (downward arrow) and "Unclench!" (upward arrow). Note the activatory character of unit reactions during the triggering and the execution phases of movements.
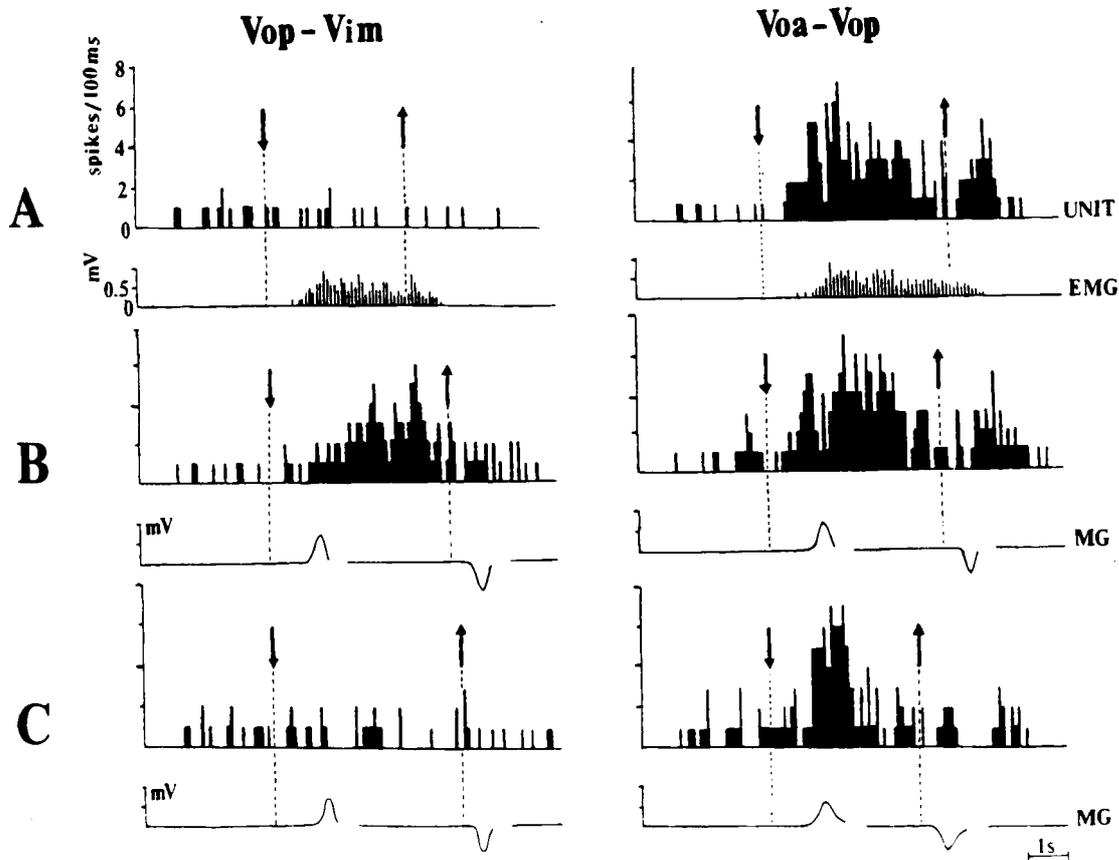
Fig. 2. Differences in EA patterns of A-type units located in the anterior (right column) and the posterior (left column) parts of the VL during the performance of wide range of verbally ordered active motor tests. Peristimulus firing rate histograms of units with averaged EMG responses or smoothed mechanograms (MG) of tested extremities during the performance of contralateral finger flexion–extension (A), lifting–lowering of the hand (B), flexion–extension of the leg (C). Other designations are as for Fig. 1. Note that neurons in the anterior VL are characterized by a high reactivity to the performance of different voluntary motor tests, while the posterior located VL units during the same movement performance revealed a somatotopic specificity of responses.

Only 13 A-cells (9%) were never activated during the movement performance or somatosensory stimulations.

The B-type units (bursting discharges firing in short trains with an unstable rhythmic 3–6 Hz pattern, 42 out of 184 studied, 23%). As a rule, B-units were recorded mainly in the anterior VL (38 out of 42 observed, 90%) or at the boundary between the Vop and the Zi nuclei (4 out of 42, 10%). The responses of the majority of B-neurons (38 out of 42 observed, 90%) to movement performances were characterized by a tonic suppression of bursts. This uniform invariable inhibition (duration 1–5 s) correlated in time with the preparation and the onset of various voluntary movements. The inhibitory unit reactions usually developed just after the verbal command presentation with a latency of 100–300 ms. During the movement realization (when the muscle contraction was maximal) and/or its after-effect a tonic inhibition of bursts was replaced by a reciprocal

activation of B-cells (90%) with the stabilization of the burst rhythmicity (80%). Typical examples of such responses are shown in Fig. 4. The repetitive motor test performances did not usually provoked EA pattern modifications but was accompanied by a decrease in the duration of inhibitory responses as well as by a reciprocal gradual increase of the frequency of burst sequences (approximately to 0.5–1.0 Hz), the number of spikes in a burst and the growth of the synchronization of discharges as a rebound effect.

As a rule, B-units showed a high reactivity also to the presentation of different somatosensory or sensory stimulations. Their EA pattern was characterized by the uniform inhibition of bursts during the performance of different functional tests (the active and passive movements of upper and lower limbs of contra- and ipsilateral side, opening and closing the eyes, etc.), displaying more pronounced non-specific EA properties compared to A-units. Four B-cells of the VL (10%) did not react to any forms of stimulation.
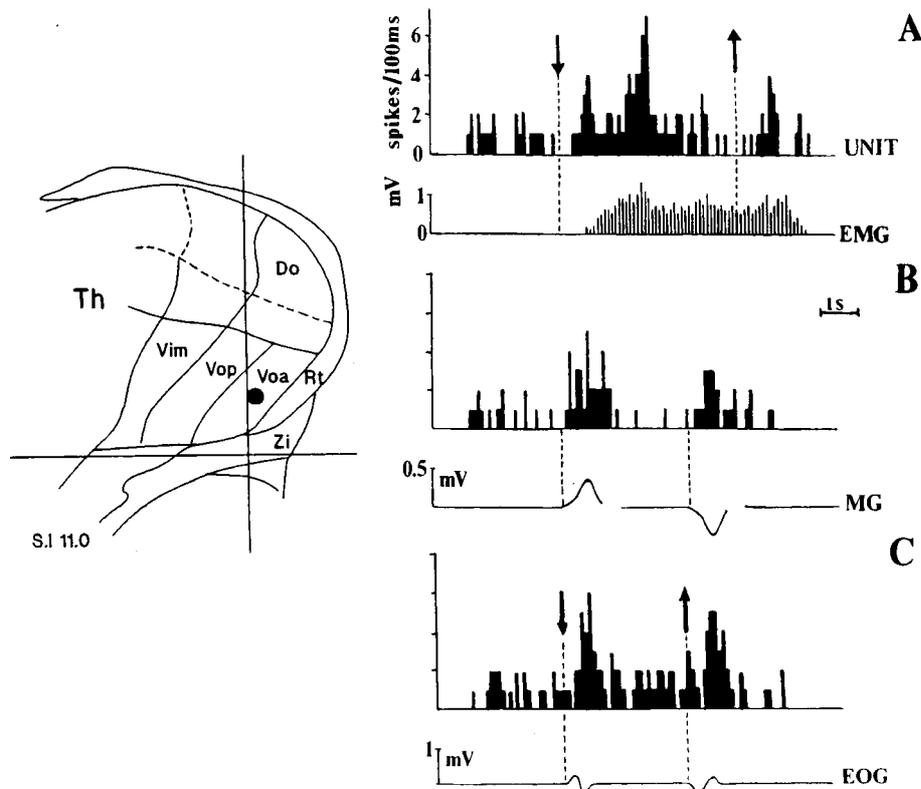
Fig. 3. Responses of a VL neuron of A-type during the performance of active finger flexion–extension (A), passive wrist flexion–extension (B), opening–closing the eyes (C). The downward and upward arrows mark the beginning and ending of tests. Other designations are as described for Figs 1 and 2. Note that the same VL neuron is activated by different stimulations reflecting the convergent polyfunctional nature of this A-unit.

Principal component analysis of evoked activity patterns of ventrolateral neurons in relation to functionally different phases of voluntary movements

The structure of the unitary responses of the two cell types of VL neurons was examined with the PCA in relation to the onset of the EMG activity and to the verbal command presentation producing a finger movement (flexion and extension). The PCs of responses of A- and B-units in the anterior and the posterior areas of the VL are shown in Fig. 5.

The EA patterns of A-units in the anterior VL (14 out of 19 analysed with PCA) were represented by two excitatory components (A-PC1, A-PC2) which correlated with activatory neuronal reactions during the triggering and the execution phases of movements (Fig. 5). The first premotor component A-PC1 (eight out of 14 studied cells) correlated in time with the phase of movement preparation. It always preceded the voluntary movement before the beginning of the initial EMG changes with a latency of 400–700 ms. Its eigenvalue was 0.15–0.2, which is a sign of instability of component A-PC1. The second stable prolonged motor component A-PC2 (10 out of 14 studied cells) appeared during the initiation and mainly during the movement execution and corre-

lated with the maximal muscle contraction. Its duration was about 1 s, the eigenvalue varied between 0.5 and 0.7.

The EA patterns of A-units in the posterior VL (5 out of 19 analysed with PCA) had only one prolonged stable excitatory motor component A-PC2. It corresponded only to the phase of movement execution (Fig. 5). Its duration was 1 s. The eigenvalue was 0.8, which indicates the striking stability of this motor component A-PC2. It revealed close correlations with the EMG changes.

The EA patterns of B-units (six out of eight analysed with PCA) had two main components (Fig. 5). The first premotor component B-PC1 correlated in time with the movement preparation and the beginning of EMG changes and corresponded to the prolonged suppression of bursting B-units. Its duration was 1.0–1.5 s, the eigenvalue was 0.2–0.3. This inhibitory component B-PC1 coincided with the appearance of activatory responses of A-units (component A-PC1). The second motor component B-PC2 correlated in time with the movement execution as well as with the phase which followed the motor act. Its duration was about 1–2 s. The B-PC2 showed stability, its eigenvalue varied from 0.4 to 0.6. This motor excitatory component B-PC2
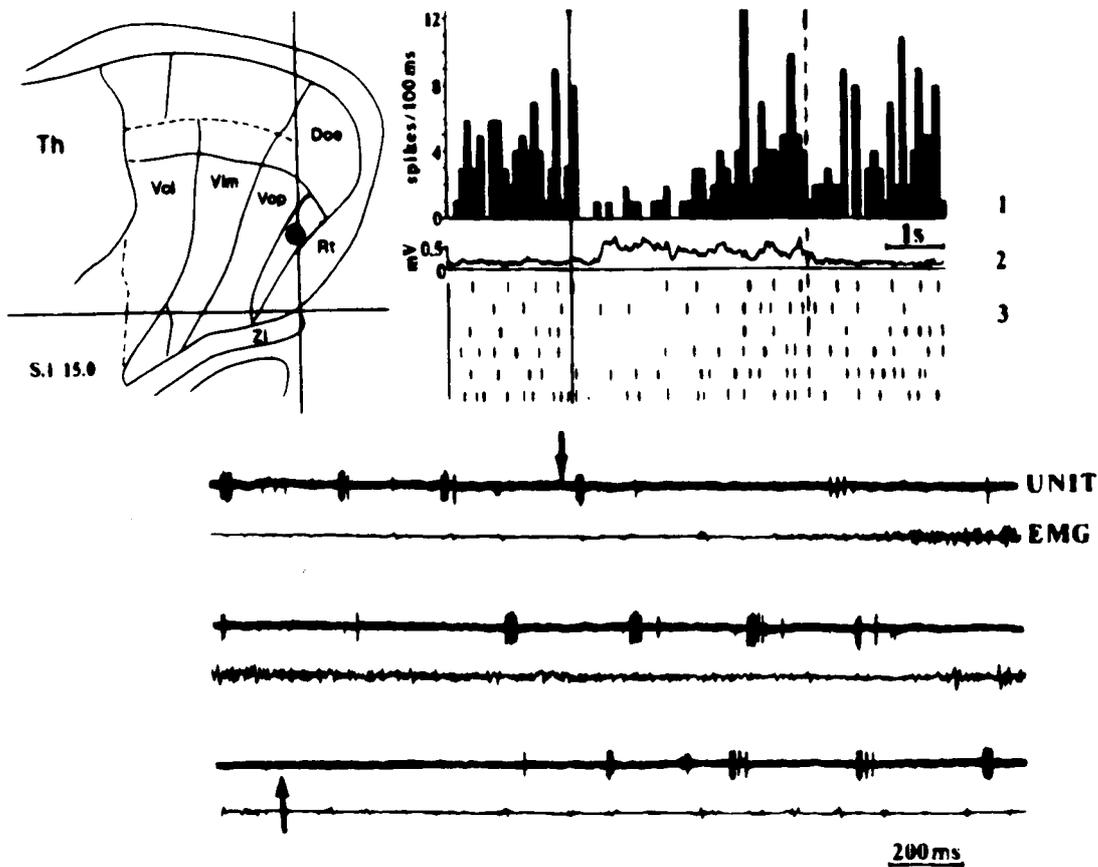
Fig. 4. EA pattern of a VL neuron of bursting B-type during the verbally ordered voluntary movement performance (finger flexion–extension). Designations are as described for Fig. 1. Note the complex configuration of EA of bursts pattern of B-unit: the inhibition of bursts corresponding to the triggering phase of movement and the reversal activation of spike discharges and the stabilization of rhythmicity corresponding to the movement execution phase.

corresponded to a postinhibitory activation of bursting B-units and coincided with activatory reactions of A-units (component A-PC2). As mentioned above, the B-type of units and consequently the B-PC1 and B-PC2 components we observed mainly in the anterior VL.

Thus, the following correlations between the EA components during the functionally different phases of voluntary movement performances have been shown: (i) during the triggering phase of voluntary movements (preparation and initiation) a stable tonic activation of A-units (premotor component A-PC1) correlates negatively with a tonic suppression of bursting B-units (premotor component B-PC1); (ii) during the movement execution, especially, during the apex of muscle contraction and/or its after-effect a prolonged positive synergic co-activations of A- and B-units were observed (motor components A-PC2 and B-PC2).

Interneuronal relationships

Using methods of the PSC matrices and spectral analyses we studied the interneuronal relationships which appeared in adjacent A- and B-units recorded simultaneously with EMG changes during the voluntary movement performance as well as during its after-effect. Dynamics of transient interconnections during the triggering and the execution phases of voluntary movements (flexion and extension of contralateral fingers) are presented in Fig. 6A and B.

A synchronous activation of two adjacent A-units (10 out of 18 pairs studied) during the movement preparation appeared at the time of premotor component A-PC1. This transient synergy between pairs of A-cells is shown in PSC matrices by the low unstable positive cross-correlations appearing before the onset of EMG changes (Fig. 6A). The more stable high synergy of cross-correlations was observed at the time of the motor component A-PC2 during the maximal muscle contraction up to 1 s in duration (13 out of 18 pairs studied).

As shown in Fig. 6B, the appearance or the significant increase of positive transient interconnections between two adjacent bursting B-units (five of eight pairs studied) was observed both during the preparation and the onset of movements as well as during the muscle contraction and/or its after-effect
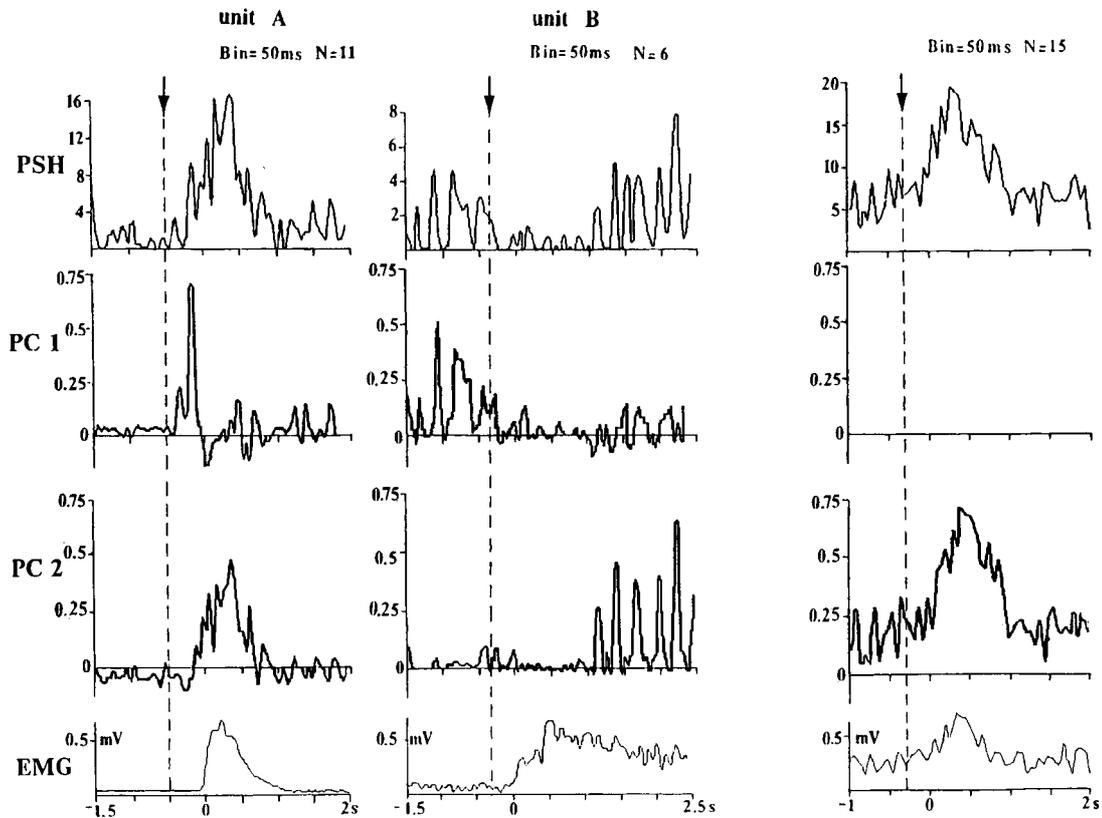
Fig. 5. Differences in principal components of responses of A- and B-neurons in the anterior (two left columns) and the posterior (right column) parts of the VL during the triggering and the execution phases of verbally ordered voluntary movements (finger flexion). Peristimulus firing rate histograms of unit responses (PSHs), normalized meanings of two principal components of responses (PC1, PC2), averaged EMG of contralateral finger flexors. The arrows mark the time presentation of verbal commands "Clench your fist!". The start moments of PCA analysis correspond to the beginning of EMG changes. N, number of averaging. Note that in the anterior VL principal components of unit responses during the triggering phase of movements are represented by the excitatory component of A-units (A-PC1) and the inhibitory component of B-units (B-PC1), while during the phase of movement execution they are represented by synergic coactivations of A- and B-cells (A-PC2 and B-PC2); on the contrary, in the posterior areas the A-unit responses are represented by only one excitatory component corresponding to the phase of movement execution (A-PC2).

(six out eight pairs studied). These transient positive connections between cells were correlated in time with the inhibitory premotor B-PC1 and the excitatory motor B-PC2 components.

The study of dynamics of interneuronal relationships by spectral analysis (92 pairs of VL cells) showed that the coherent positive interneuronal correlations between adjacent of pairs of A- (39 out of 57 pairs studied), B- (12 out of 15 pairs studied) and A- and B-cells (12 out of 20 pairs studied) at the apex of movement performance and/or during its after-effect coincided with the appearance of both the transient rhythmic 5 ± 1 Hz activity for non-rhythmic A-cells and the stabilization of rhythmicity at the same frequency for bursting B-cells. As shown in Fig. 7, after the motor test performances we observed the appearance of a clear central peak on the spectrograms at the frequency of 5 ± 1 Hz. This indicates the appearance of a marked tendency to fire in synchronous 5 ± 1 Hz rhythmicity which is accompanied by

the above mentioned transient cross-correlations between neighbouring units in pairs of A-, B-, and in pairs of A- and B-types (Fig. 6). The duration (from 1–3 s up to 5–10 s) of cross-correlations at the frequency of 5 ± 1 Hz during repetitive motor tests significantly increased (14 out of 63 pairs studied, 22%). These transient interneuronal cross-correlations at the frequency of 5 ± 1 Hz seem to reflect a functional coupling between neuronal spike trains of adjacent cells appearing in the VL after voluntary movement performances. It should be noted that a weak tendency to synchronization of clusters of bursts belonging to different adjacent cells was found out in the spontaneous activity of B-cells at rest.

DISCUSSION

The functional approach combined with micro-electrode recording and elaborated methodology of
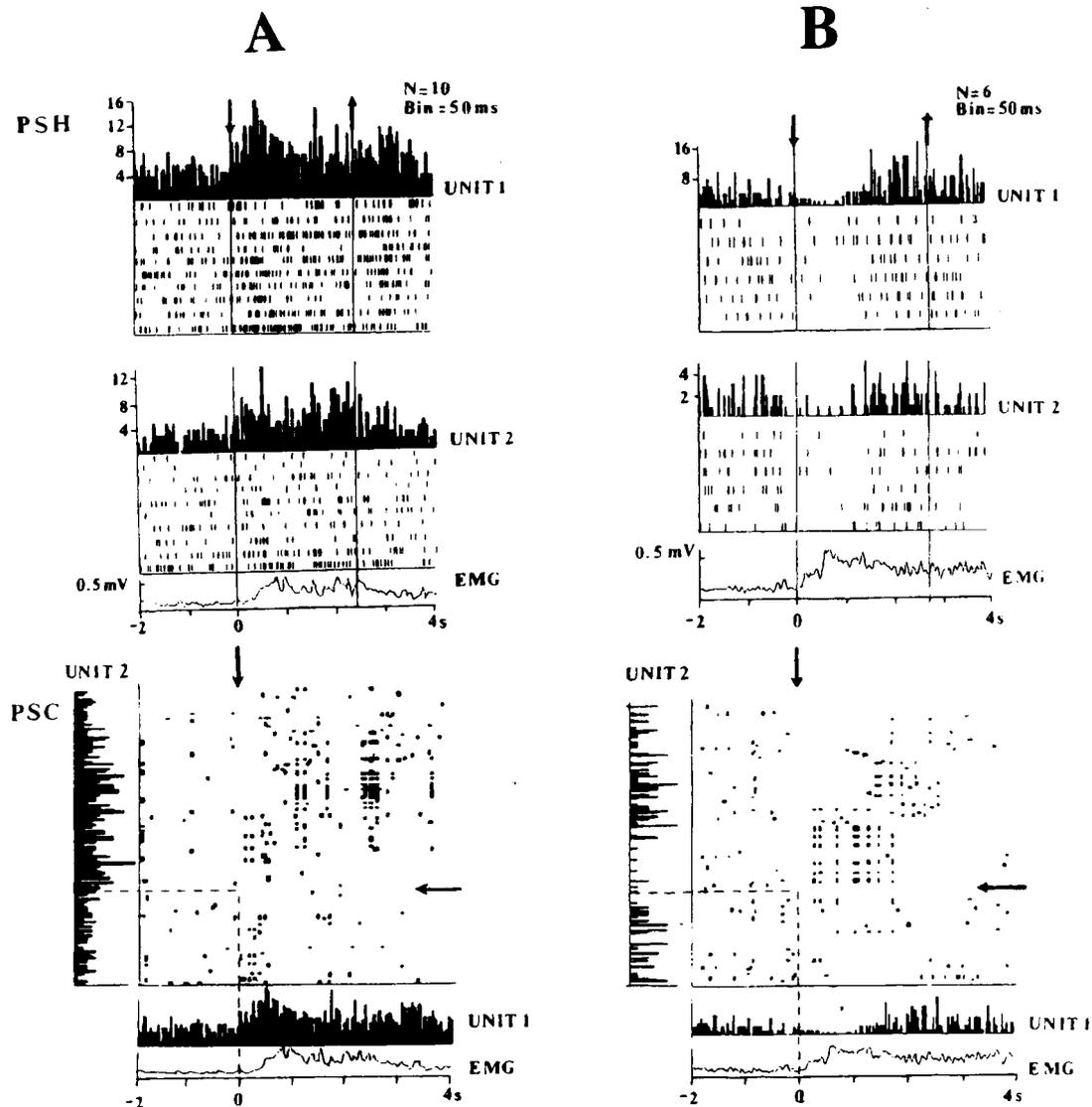
Fig. 6. Dynamics of interneuronal relationships between adjacent two neurons of A-type (left column) and B-type (right column) during the performance of verbally ordered voluntary movement (finger flexion). Peristimulus firing rate histograms of responses PSH, rasters, averaged EMG of contralateral finger flexors, peristimulus cross-correlation matrices of units (PSC). The appearance of positive cross-correlations between adjacent cells are marked by black dots. The arrows mark the time of imperative accents of verbal commands "Clench your fist!" (downward arrow) and "Unclench!" (upward arrow). The start moments of PSC matrices construction correspond to the beginning of EMG changes. N, number of averaging. Note that the triggering and the execution phases of voluntary movements are accompanied by the appearance of a positive transient cross-correlations in pairs of A-type and B-type units.

verbally ordered functional cell testing provided new information on the functional organization and the role of the human VL.

Characteristics of evoked activity patterns of two types of ventrolateral neurons

The quantitative analysis of evoked activity patterns of VL neurons showed the differences between responses of A- and B-cell types during functionally different phases of verbally ordered voluntary

movements and also during some somatosensory stimulations

The A-type units responded by a tonic activation which had the multiphasic, mainly three-phasic configuration. A tonic increase of spike frequency was closely correlated with the triggering (preparation, initiation) and the execution (the period of muscle contraction) phases of a movement as well as with its after-effect as a rebound late excitation. The termination of a movement was accompanied by diverse phasic inhibitory changes of cell activity. The evoked
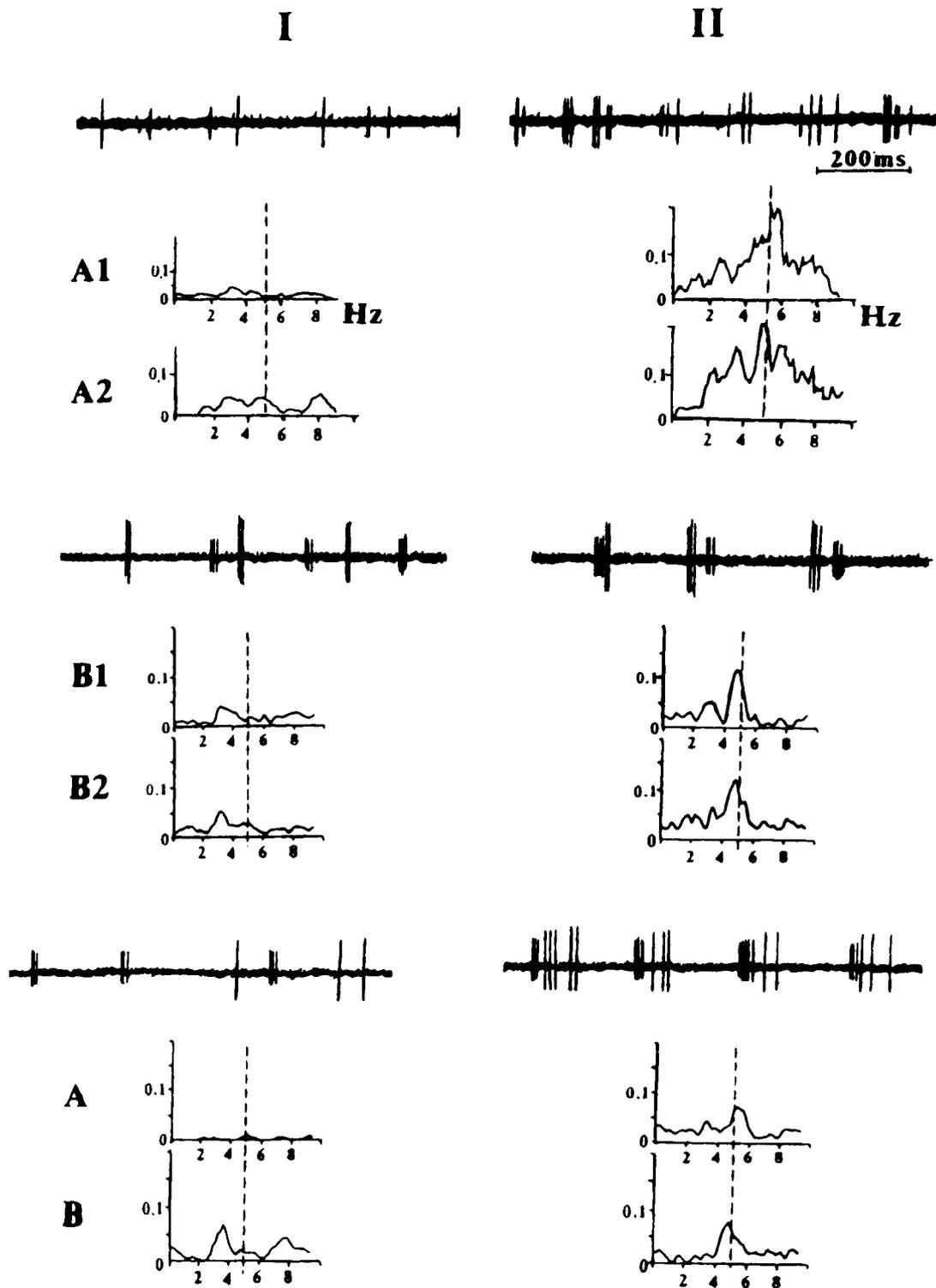
Fig. 7. Cross-correlations at the 5 ± 1 Hz frequency between adjacent VL units in pairs of A-, of B- and in pairs of A- and B-types before (I) and after the performance of repetitive voluntary motor tests (II). The following traces for two adjacent cells are presented, respectively, unit activity and firing rate frequency spectrograms: abscissa=frequency (Hz), ordinate=frequency spectrogram (bin 50 ms). Note that the coherent positive cross-correlations at the range of 5 ± 1 Hz in pairs of A-, of B- and in pairs of A- and B-units appeared after the motor test performances.

activity to repeated motor tests demonstrated no habituation. Moreover, a progressive accentuation of a rebound late activation was accompanied by an increase in firing rate of discharges (57%). On the contrary, the responses to repeated somatosensory stimuli rapidly reduced. In small cases (7%) units, located at the boundary between the VL and the RT nuclei, reacted also to the presentation of verbal command provoking the starting of a voluntary movement. This group of convergent neurons, which we termed ''triggered verbal command'' units, was described for the first time in the RT and some non-specific and associative subcortical integrative structures of the human brain in previous papers.[61–63,66,67]

The bursting B-type units located only in the anterior VL demonstrate during movements the complex configuration of EA patterns: a tonic inhibition of bursts corresponding to the triggering phase of movement, a reversal postinhibitory activation of burst discharges and a stabilization of the rhythmicity that appears at the apex of muscle contraction and/or during its after-effect. The majority of B-units responded also to somatosensory stimulations by a uniform tonic suppression of bursts. It should be noted that B-type neurons present more non-specific features than A-cells.

The results confirm in part the data found previously by other authors in the human ventrobasal thalamic nuclear group in dyskinetic patients. Certainly, A-type neurons are the ''voluntary movement'' cells which activity increased or decreased in relation to movements.[15,28,33,44,45,61–64,80,82] Tasker et al.[80] and Lenz et al.[44,45] on the basis of the analysis of functional properties related to sensory and motor events along with the results described by other investigators[3–5,33,52–55,62,63] classified thalamic neurons, located in ventrocaudal, Vim and Vop nuclei, into four types: (i) sensory cells; (ii) voluntary cells; (iii) combined cells which activity related both to the somatosensory stimulation and the active movement; (iv) no-response cells. Many of the cells included in this classification exhibit also tremor-frequency activity (tremor cells). The changes of unit discharges before and/or during active movements were observed also in primates in the VL and the ventral posterolateral pars oralis nuclei.[8,19,21,30,36,46,50,78] According to Hirai and Jones[27] these subcortical structures in primates correspond to the human Vop and Vim thalamic nuclei.[26]

Our present results demonstrate the existence in the human VL (consisting of Voa and Vop nuclei in Hassler's nomenclature[26]) of two (A and B) functionally different types of neurons, whose activity reacted differently during voluntary movements and also during somatosensory stimulations. According to the criteria of their SA (see the companion paper[69]) and EA patterns the differences of responses of two above cell types during the triggering and the execution

phases of a voluntary movement indicate the functionally different role of A- and B- units in mechanisms of the motor signal transmission in the VL. It should be noted, however, that together with a number of differences between activities of A- and B-neurons, the common convergent polyfunctional features of these cell types during active movements were found. This is in agreement with the data found in the animal VL.[1,2] A possible origin of the above two types of VL neurons based on the analysis of their intrinsic structure of SA patterns is described in the companion paper.[69]

Relations of principal components of unit responses to the triggering and the execution phases of voluntary movements

The PCA of the EA patterns of A- and B-cells during different phases of motor test performances has shown differences of the main PCs of reactions that correlate with the triggering and the execution phases of voluntary movements.

(i) The A-PC1, an early tonic activation of A-units anticipates the initial EMG changes and correlates with the phase of movement preparation. It presents mainly in the anterior VL

(ii) The B-PC1, a tonic inhibition of bursting B-units during the movement preparation and initiation exists in the anterior VL only.

(iii) The A-PC2, a tonic longer activation of A-units correlates mainly with the movement execution and the EMG manifestation. It presents both in the anterior and the posterior VL.

(iv) The B-PC2, a tonic activation of B-units correlates with the apex of muscle contraction and/or its after-effect. It presents in the anterior VL only. Contrary to the triggering phase, both the A-PC2 and B-PC2 components showed synergic co-activations during the movement performance which may be due to increased ascending afferent influences.

The appearance of temporally correlated premotor components A-PC1 and B-PC1 during the triggering phase suggests their close relation to the stages of the preparation and initiation of various voluntary movements. Taking into account the uniform invariable non-specific form of anticipatory A- and B- unit responses observed in the anterior VL, we believe that these associated neuronal alterations may reflect the integrative ''triggered'' thalamocortical processes connected with the processing and programming of some generalized parameters of a motor signal and not with the performance of a concrete forthcoming movement. From this point of view the anticipatory activations of A-cells (A-PC1) seem to reflect the dominant descending cortical command signals preceding the starting of an intended movement. Simultaneously developing inhibition of bursting B-cells during the movement preparation and initiation (B-PC1) seems to reflect

the descending corticothalamic drives as well as the pallido-Voa and the intrathalamic RT-Voa influences.[8,13,31,32,34,37,38,40,48,50,57,60,73,76,77,79,81,84] Our suggestion is in agreement with recent human electroencephalographic and magnetic resonance imaging studies.[10,23,39,75] We have found similar anticipatory neuronal responses during the performance of identical verbally guided motor tests not only in the VL but also in some human subcortical structures—the non-specific and associative thalamic nuclei and the basal ganglia.[61–63,65–67]

During the phase of movement execution the PC analysis has shown other characteristics of the EA patterns of A- and B-cells revealing synergic activations. The most stable motor component of A-units (A-PC2) directly correlated with the muscle contraction. It seems to reflect both the descending signals (providing the current motor control from cortex) and the ascending (cerebellum, reticular, pallidal) afferent feedback influences that carry out the correction of a movement. As has been mentioned earlier, during the maximal muscle contraction bursting B-units located in the anterior VL have a synergic co-activation with A-units and the bursts are stabilized. This excitatory component B-PC2 could be attributed not only to ascending afferent influences but also to the intrathalamic RT-Voa connections and to the local interneuronal relationships between A- and B-units in the VL. The latter assumption is in agreement with what was found in animal experiments.[77,79]

Functional significance of interneuronal relationships in the motor signal transmission during voluntary movements

The cross-correlation analysis of evoked activities in pairs of adjacent A-and B-cells has shown the appearance of transient short-lasting interneuronal connections during the triggering and the execution phases of a voluntary movement. The simultaneous appearance of both a transitory proceeding coherence at the 5 ± 1 Hz frequency and cross-correlations in pairs of adjacent A- and B-units after repetitive motor tests also suggest that the local interconnections exist between adjacent cells after the resulting movement performance as a rebound effect. These interconnections should be provoked by the different inflows coming from descending cortical and ascending afferent influences as well as by parallel interstructural neuronal circuits.

This finding permits us to conclude that the appearance of transient neuronal relationships during the triggering and the execution phases of voluntary movements seem to reflect a collaborative concordant signal processing of two types of convergent units.

The activatory reactions of A-units (A-PC1 and A-PC2 components) during the triggering and the execution of a movement seem to transmit a motor signal. The simultaneous inhibition of bursting B-cells, which appeared during the preparation and the starting of a movement (B-PC1 component) seems to facilitate this signal transmission. The opposite synchronous synergic co-activation of B-units during the maximal muscle contraction and/or its after-effect (B-PC2 component) may play a modulatory role allowing the final performance and corrections of a movement. It may be assumed that the positive or negative character of transitory proceeding interconnections in A- and B-populations are predetermined by the above two main functionally different phases of a voluntary movement. Such transient correlations between two similar types of convergent neurons during the performance of verbally ordered movement were described previously in the human RT.[67]

Functional differences between the anterior and the posterior parts of the human ventralis lateralis nucleus in the signal transmission during psychomotor behaviors in man

The study of spontaneous (see companion paper[69]) and evoked activity patterns of units has revealed some functional differences in the neuronal organization of the anterior (Voa) and the posterior (Vop) parts of the human VL, in particular: (i) the differences in the localization of A- and B-neurons; (ii) the differences in the latency and the relative somatotopic specificity of responses; (iii) the differences in the EA patterns of VL units during motor test performances with more or less accentuation and stability of the triggering premotor and the motor components of responses.

These Voa-Vop functional differences suggest that neurons located in the anterior and the posterior areas of the VL play the different functional role in the motor signal transmission during the triggering and the execution phases of a voluntary movement (see also above sections). This fits well with the morphological and physiological data showing that the inputs to the Voa and the Vop nuclei are coming from different levels.[8,31,32,34,37,38,48–50,57,60,81,84]

The more expressed intensity of the premotor components of A- and B-unit responses during the triggering phase of a movement observed in the anterior VL (Voa) may indicate the relation of these regions not only to the motor but to the cognitive attentional functions forming psychomotor behaviour in man. The evidence of the cognitive, especially, attentional components in the control of verbally ordered movements is confirmed by our previous data which had shown that the verbal command as the ''trigger'' signal plays a significant role in the switching mechanism of motor and simplest mental acts in some non-specific and associative nuclei of the human thalamus.[62–64,66,67] Our assumption fits well with recent clinical observations showing in

parkinsonian patients the deficit in both the cognitive attentional control and the preprogramming of movement.[11,14,18,71]

The interesting finding described here is also the excitatory character of A-unit responses (A-PC1 and A-PC2) in the anterior VL (Voa) during the triggering and execution phases of movements. Taking into account inhibitory circuits mediated by pallidal-Voa connections[51,84] and an inhibitory deficit of parkinsonian pathology,[14,70,74,83] the activatory character of EA patterns of A-unit responses in Voa areas seem to reflect the dominant excitatory corticothalamic influences along with the simultaneously developing a decrease or removal of the inhibition (disinhibition) coming from the globus pallidus, internal segment (GPi), the substantia nigra pars reticulata (SNr), the RT and brainstem sources during the movement performance. This is in agreement with the disinhibitory striatal mechanism proposed by several authors.[8,12] The results described recently by Parent and Hazrati[57] suggest that the external segment of the globus pallidus via its projection to the GPi/SNr may produce a disinhibition of thalamocortical cells of the ventroanterior/ventrolateral (VA/VL) thalamic complex which allows movement to be executed.

As mentioned above, in the posterior VL we have observed only the motor components of A-units. They may be due to direct inputs coming from cerebello-Vop connections.[8,34,37,38,81]

Mechanism and relation of the rhythmic 5 ± 1 Hz neuronal phenomenon to the motor control and the parkinsonian tremor

The quantitative analysis of SA and EA patterns of two types neurons in the VL helped to clarify more precise the mechanisms of 5 ± 1 Hz phenomenon connected with pathological tremorogenic system of parkinsonian patient described by several authors.[3–5,10,33,45,51,54,55,61–63,80,82] In our previous studies we have found for the first time in the VL and the basal ganglia in patients with or without tremor (rigid forms of Parkinsonism, torticollis) the cell populations characterized by a ''latent'' rhythmic 5 ± 1 Hz oscillatory tendency which was accentuated by repetitive motor executions. These findings allow us to suppose that this transient rhythmic 5 ± 1 Hz phenomenon may depend on common mechanism related to both the motor control and the generation of parkinsonian tremor.[61–65]

The data presented show that two main factors may underlay this phenomenon: the appearance of a synergic coactivation and the coherence at 5 ± 1 Hz frequency between A- and B-units due to both an increase of endogenous and exogenous afferent feedback inflows and a postinhibitory activation of B-units due to a rebound effect of movements. It also seems significant that there is a specific ability of A-type neurons to react during voluntary movements

by transformation of their SA unitary irregular pattern into a transient rhythmic burst-like discharges with two different intrinsic mechanisms of firing modification observed in the anterior and the posterior VL (see companion paper[69]). It might be produced by both a decrease of inhibitory intrathalamic GABAergic influences (through pallidoVoa and RT-Voa connections) and a excitatory afferent inflows (through cerebello-Vop connections). On the whole, all above mentioned data may provide a clue to understanding both the motor signal transmission mechanism and the generation of parkinsonian tremor. Our results seem to justified the view that parkinsonian tremor is an example of a repetitive motor behavior driven by the activity of central oscillatory mechanisms.[9,16,58]

Although the neuronal activity described was studied in parkinsonian patients with motor dysfunctions our present and previous data allow to support the view that these neurophysiological data may reflect general physiological processes in the human VL rather than motor abnormality. This may be substantiated by the following data: (i) similar rhythmic 2–5 Hz activity of B-type of units was recorded in the VL and some other thalamic nuclei in patients without tremor—akinetic and rigid forms of Parkinsonism, torticollis, cerebral palsy, central pain;[3–5,43,53,54,67,68] (ii) similar rhythmic bursts were observed in animal VL;[36,47] (iii) similar rhythmogenic patterns of responses of convergent neurons of A- and B-types during verbally ordered voluntary movements we observed not only during the voluntary movements but also during the performance of some mental acts.[62,65–67]

From the practical point of view the data obtained could be useful as a functional guide in the choice of optimal lesion in the ventral thalamic nuclear group during stereotactic interventions. The identification of neuronographic markers in the VL is important for the treatment of mixed forms of Parkinsonism since they may indicate that destruction predominantly in the anterior VL which disturb pallidothalamic connections is the most effective target in rigid parkinsonian patients.[25,51,54,56] Taking into account the relation of these neuronal areas not only to the motor but also to the cognitive processes, application of these markers made will allow to reduce the volume of damage and reduce side effects.

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