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Neuronal Activity of the Subthalamic Nucleus in Patients with Parkinson's Disease

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Abstract—The discharge activity of 637 neurons of the human subthalamic nucleus (STN), which were extracellularly recorded during twelve stereotactic surgeries in patients with Parkinson's disease, has been analyzed. On the basis of the parameters of interspike intervals (ISIs), we have distinguished three major patterns of spontaneous neuronal activity: bursting neurons, regular tonic and irregular tonic neurons. Parametric analysis has enabled us to determine the values of basic parameters in the activity of these three distinguished types of neurons. It has been shown that the representativeness and the activity parameters of three different patterns change in the dorsoventral direction of the STN from the motor to the associative regions. The results will allow researchers to perform targeted search of pathological neuronal activity patterns associated with the motor symptoms of Parkinsonism.

Keywords: Parkinson's disease, basal ganglia, subthalamic nucleus, microelectrode recording, activity of single neurons

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The subthalamic nucleus (STN) is a part of the basal ganglia system, a group of subcortical nuclei constituting the functional system for controlling movements and motivation-related aspects of behavior. According to the classical scheme of the basal ganglia organization [1], projections between nuclei of the basal ganglia form two counteracting circuits: the excitatory "direct" pathway running directly from the corpus striatum to the internal segment of the globus pallidus and the inhibitory "indirect" pathway passing from the corpus striatum to the internal segment of the globus pallidus through two supplementary formations: the external segment of the globus pallidus and the subthalamic nucleus (STN). It is believed that a balance between projections of direct and indirect pathways is necessary for proper performance of motor tasks; in the case of their imbalance, motor disorders, such as forms of dyskinesia or Parkinsonian syndrome, may develop [2, 3]. As a part of the indirect pathway, the STN has afferent projections from the external segment of the globus pallidus (inhibitory projections), as well as efferent projections to the external and internal segments of the globus pallidus (excitatory projections) [2, 3]. In addition, direct excitatory projections run from the motor areas of the brain (the motor, premotor, and supplementary motor cortices) [4] to the STN, which are referred to as the "hyperdirect" pathway and which are necessary for a prompt inhibition of movements being performed. Apart from the described projections running from the globus pallidus and the motor areas of the cortex, the STN receives dopamine projections from the substantia nigra, glutamate projections from the thalamus (the centromedian-parafascicular (CM-Pf) nucleus), and, most probably, acetylcholine projections from the pedunculopontine nucleus [5], although their actual role in the STN activity modulation remains unclear.

Studies based on the tractographic methodology and functional magnetic resonance imaging (fMRI) have shown that the STN consists of three functional areas: the limbic area is located in the frontal part of the nucleus, the posterior part locates the motor area, and the associative area is located between the aforementioned two ones [4, 6]. The STN is structurally homogeneous and predominantly consists of the bodies of glutamatergic projection neurons, however, as has been found with immunohistochemical staining, the nucleus also contains interneurons, which account for nearly 7.5% of its total neuronal population, although they are predominantly located in the associative area [5, 7].

One of the principal STN functions is believed to be suppression of undesired movements through the indirect or hyperdirect pathway [8]. There are also

indications that the STN locates the processes of behavior selection in a situation of disputed choice. In addition, the nucleus takes part in connecting cognitive processes, such as inhibitory control and error monitoring, with behavior [9]. The study of alterations in the activity of the STN motor area in response to movements has detected the somatotopical organization of this structure. Neurons sensitive to hand movements were located more dorsally and laterally than neurons altering activity in leg movements. Neurons associated with the stomatognathic system were located in the central part of the sensorimotor area in the nucleus and more ventrally than "limbic neurons" [10].

The normal neuronal activity in the human STN remains unknown due to ethical considerations, although we have data about neuronal activity in the intact STN in primates [11, 12] and the STN activity in patients with Parkinson's disease (PD) [13]. The average discharge activity varying from 25 to 45 spikes/s is characteristic of the STN of patients with PD, whereas the studies in primates have shown that dopamine deficiency in the substantia nigra leads to an increase in discharge activity of the STN up to 30–40 from 20 spikes/s [11, 14]. Despite the structural uniformity of the STN, microelectrode recording allows experimenters to detect substantial differences in the activity of single neurons: irregular, tonic, and oscillatory activity types [10, 15]. The data on the representativeness of different neuronal activity patterns in the STN vary considerably in different studies, depending on the method and the parameters used to distinguish the patterns. For example, various researchers assess the representativeness of bursting activity in the STN of patients with PD as 8% [13], 15% [10], or 67% [15].

For more than two decades, the STN has been serving as a target for implanting deep brain stimulation electrodes which allows to alleviate substantially the symptoms of PD [2, 3]. Despite a pronounced clinical effect of STN stimulation, the pathophysiological processes underlying the STN activity disorders are not yet understood. One model of motor dysfunctions considers pathological synchronization to be one of the most important factors that initiate the development of Parkinsonian symptoms [3, 14, 16]. Indeed, there are data that the synchronization of neuronal activity in patients with PD is significant in several frequency ranges, including, primarily, the "tremor-associated" low frequencies (about 4 to 6 Hz) and the β frequency range of 14 to 30 Hz [14, 16]. There are also indications of a positive correlation between the spectral intensity of neuronal activity in the β frequency range of 14 to 30 Hz and rigidity in patients with PD [17, 18].

Although the structure and functioning of the STN and its connections with other nuclei of the basal ganglia are now intensively studied, we still know too little particularly about the neuronal organization of the nucleus and pathophysiological alterations of its activity due to dopamine loss in patients with PD. The mechanisms behind the neuronal activity synchronization in certain frequency ranges and its relation to the pathophysiological events in PD also remain unclear. This study continues a small series of research in the human STN and aims at determining the characteristics of spontaneous neuronal activity in the STN of PD patients in detail, as well as, the specific localizations of different patterns in the STN.

METHODS

The study enrolled 12 PD patients (four men and eight women, the mean age was 57.3 ± 4.8 years, the mean disease duration was 11.9 + 4.8 years, the disease severity according to the unified Parkinson's disease rating scale (UPDRS)-III, without levodopa administration, ranged from 39 to 71 points). The indication for surgical treatment included resistance to conservative treatment, complications due to a prolonged dopamine-substituting therapy (motor fluctuations and different forms of dyskinesia). A brief outline of patients selected for the study is presented in Table 1. Before the surgery, all patients were neurologically examined, and the procedure included the assessment of the form of the disease and its stage by the Hoehn and Yahr scale, the expression of the disease symptoms prior to (UPDRS off) and after (UPDRS on) levodopa administration, as well as sensitivity to the drug. The study was approved by the Ethics Committee of the Burdenko National Medical Research Center of Neurosurgery. The patients signed their informed consent before their inclusion into the study program.

Data collection methods. The data on the discharge activity of the STN neurons were obtained by microelectrode recording during planned stereotactic surgeries at the Burdenko Center of Neurosurgery. Microelectrode recording was used to identify the STN boundaries and select the optimal trajectory for deep brain stimulation (DBS) electrodes. The surgeries were performed under local anesthesia with naropin. The calculated STN coordinates were specified by T1- and T2-weighted MRI images, using the Leksell G SurgiPlan (Elekta) software. (The RTC Coordinates: 3.5 to 4.5 mm below and 11.5 to 13 mm lateral to the CA-CP line, 1.5 to 2.5 mm posterior to the CA-CP midline). Figure 1 gives the microelectrode movement trajectories that pass through the STN in the course of surgeries. The microelectrode trajectories were located close to one another and passed through the posterior segment of the STN, in which its motor area was located.

The spontaneous activity of neurons were recorded using a navigational NeuroNav system for inserting a micro- and macroelectrode (Alpha Omega, Israel, www.alphaomega-eng.com), which was fixed to a stereotactic Leksell coordinate frame G (Elekta, Swe-

Table 1. Summary information about patients included in the study

Patient	Sex	Age	Disease duration	UPDRS III off	UPDRS III on	Equivalent dose of levodopa
1	F	54	8	55	13	1316
2	M	60	12	50	6	900
3	F	55	22	54	8	2150
4	F	62	18	68	34	3000
5	F	40	7	31	33	300
6	F	55	6	49	6	3600
7	M	49	9	39	14	1950
8	F	62	17	47	22	3310
9	F	63	11	40	10	1600
10	F	57	11	43	8	1150
11	M	53	8	59	11	1950
12	M	54	13	71	11	1250
13	F	64	8	52	15	2200

den) firmly affixed to the patient's head. Neuronal activity was extracellularly recorded in the two brain hemispheres, starting at a distance of 15 mm to the calculated target point with a 0.1- to 0.2-mm step, using tungsten microelectrodes with a resistance of 0.3–0.8 MΩ.

Data preprocessing and analysis. The study included the analysis of neurograms with stable spontaneous neuronal activity lasting for at least 10 s and containing at least 200 spikes, with good signal-to-noise ratio. At the preprocessing stage, the signal was filtered from interference and artefacts, and the activity of single neurons was sorted by the shape and amplitude of spikes, using the principal component analysis method in the Spike2 software (Cambridge Electronic Design, United Kingdom).

The obtained spike trains were subsequently analyzed using the NeuroExplorer software (Nex, United States). We determined the mean discharge frequency ("activity" of the neuron) for each isolated neuron and calculated the mean value, the median, and CV of interspike intervals (ISIs), and, in addition, builded a histogram and Poincare's reflection for ISIs, and an autocorrelogram for discharge activity of the neuron. The neuronal activity patterns were identified according to the methodology described by Steigerwald et al. [15] with modifications. To identify the bursting activity patterns, we used the asymmetry index (AI) for ISIs, which was calculated as the ratio between the median and the mean ISI. Neurons were assigned to the bursting type if the AI value was below 0.7; otherwise, neurons were classified as tonic. To distinguish between regular tonic and irregular tonic activities, the ISI coefficient of variation (CV) value was used; the activity pattern was considered regular if the CV value was below 0.85, while the remaining neurons were referred as tonic.

To analyze the bursting activity parameters in detail, we discriminated individual spike bursts by the Poisson Surprise method with the parameter of $S > 3$ [19]. We determined the frequency of bursts, the burst length, the number of spikes per burst, the percentage of spikes falling into the bursts, the length of interburst intervals (IBIs). Oscillatory characteristics of neurons were defined with a spectral analysis. The data were statistically analyzed, using the R project information processing language (the R Foundation). The mean values are represented in this article as the median value and 25 and 75% quartiles. The statistical significance of differences was evaluated using the nonparametric variation of the post-hoc dispersion analysis with Tukey's test at the significance level of 0.05.

RESULTS

In the course of 12 stereotactic surgeries, we isolated 637 single unit in the STN, and recorded and analyzed spontaneous activity of 23 to 123 neurons for each patient in the two hemispheres. The STN neurons significantly differed from one another in the level of discharge activity, patterns and oscillatory characteristics, and the activity of neurons significantly varied both within a particular nucleus and between patients. On average, the length of recording per single unit was 18 s (13 to 28 s) and contained, on average, 659 (387 to 1084) spikes.

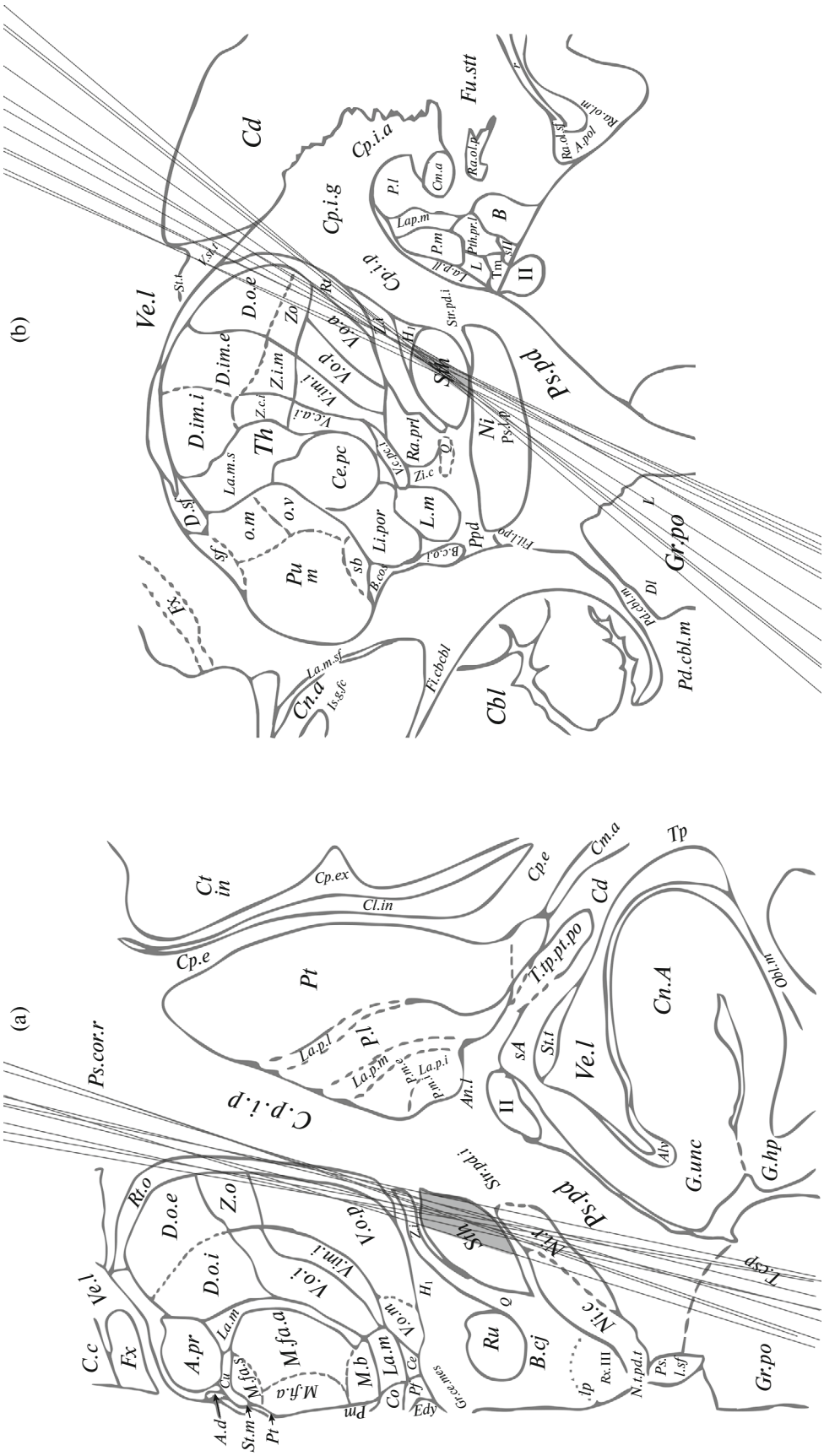

Fig. 1. Microelectrode movement trajectrories through the subthalamic nucleus during stereotactic surgeries: (a) frontal section, (b) sagittal section.

Table 2. Characteristics of different patterns for spontaneous neuronal activity in the STN. The table presents median values (lower quartile–upper quartile)

Neuron type	Bursting	Irregular tonic	Regular tonic
Representativeness of patterns	68% (61.8–69.2%)	17.5% (8.0–28.2%)	9.5% (5.0–13%)
Discharge frequency, spikes/s	34.9 (24.4–49.9)	41.6 (27.1–58.6)	45.5 (36.8–64.7)
Asymmetry index (AI)	0.58 (0.50–0.64)	0.73 (0.72–0.75)	0.82 (0.79–0.84)
Coefficient of variation (CV) of ISIs	1.22 (1.1–1.39)	0.94 (0.90–1.02)	0.75 (0.63–0.80)

Studying spontaneous activity in neurons, we have distinguished three typical patterns of neuronal activity, as has been described in the methodology: bursting, irregular tonic and regular tonic patterns (Fig. 2, 1–3). Each of the distinguished types of neurons has specific characteristics in the distribution of ISIs in the ISI histogram, Poincaré map, and the autocorrelogram (Fig. 2). As the neurogram in Fig. 2 (1a) shows, the bursting activity pattern was represented by compactly located groups of spikes separated by pauses, i.e., interburst intervals (IBIs). Clusters of points formed squares on the Poincaré map (Fig. 2, 1b); the densest cluster was located at the left inferior angle which corresponded to intraburst intervals, whereas groups of points at the right inferior and left superior angles corresponded to IBIs. The histogram of ISIs (Fig. 2, 1c) was represented by a unimodal Poisson-like distribution of ISIs with a marked narrow 4–6 ms mode. Several equidistant peaks in the autocorrelogram (Fig. 2, 1d) confirmed the presence of rhythmicity in the activity of this neuron.

A typical example for the activity of irregular tonic neurons is presented in Figs. 2 (2a–2d). As the neurogram fragment shows, the activity of these neurons was represented by randomly interchanging dense and rarified segments of spikes with arbitrary lengths. The ISIs of this type of neurons formed a single fuzzy cluster of points on Poincaré map (Fig. 2, 2b). The histogram of ISIs had a Poisson-like distribution with a wide mode of 8 to 15 ms, while no significant periodic modes were identifiable in the autocorrelogram (Fig. 2, 2c–2d).

The third activity type shown in the neurogram in Fig. 2 (3a) was represented by a regular spike flow without any densification or rarefication. The Poincaré map points formed a single oval-shaped cluster. The ISI histogram had a bell-like distribution with a mode of 8 to 12 ms (Fig. 2, 3c). The autocorrelogram was plateau-shaped and did not contain any peaks (Fig. 2, 3d).

Table 2 displays data on the distribution of the activity and key parameters of the identified types of neurons. The larger part of neurons (75%) was characterized by a bursting activity pattern, whereas irregular tonic neurons resulted in 17% of the total STN neuronal population and only 8% of neurons left for regular tonic cells. As shown in Table 2, tonic neurons significantly differed from bursting ones not only in terms of AI and CV, but also in the mean discharge frequency, i.e., in the intensity of discharge flow. Bursting neurons had a low mean discharge frequency (almost 35 spikes/s), a low AI value and high variability of ISIs. Irregular tonic neurons had a higher discharge frequency (almost 42 spikes/s), a high AI and lower variability of ISIs. Tonic regular neurons, having a comparable frequency of discharges (almost 45 spikes/s), were distinguished in the maximum AI value and minimum variability of ISIs.

Some additional parameters of isolated bursts were applied to characterize the bursting activity pattern. Using the Poisson Surprise method in correspondence with the described methodology, we detected 4 to 17 bursts (nine bursts, on average) in the time interval of recording from 16 to 32 s (22 s on average) for each spike train. Thus, the number of bursts per second varied from 0.21 to 0.65. The proportion of spikes recorded within bursts constituted, on average, 11.7% (6.3 to 18.6%), the mean number of spikes per burst was 11.8 (9.0 to 15.7). The intraburst ISI was 6.4 ms (4.9 to 8.7 ms), the interburst interval lasted for 1.43 s (0.84 to 2.53 s).

We also studied the representativeness of neurons oscillating in the β-frequency range (14 to 30 Hz). In total, 28 neurons (5.9%) with expressed peaks were detected in the β range in the spectrogram, and from 0 to 6 neurons with β activity were counted per patient. These neurons were characterized by a high mean discharge frequency (56 spikes/s, from 36 to 73 spikes/s), whereas the AI and CV of ISIs corresponded to the mean values for the bursting type of neurons (the median values were 0.53 and 1.18, respectively).

Analysis of neuronal activity along the microelectrode movement trajectory has shown heterogeneity in the distribution of different patterns from dorsal to

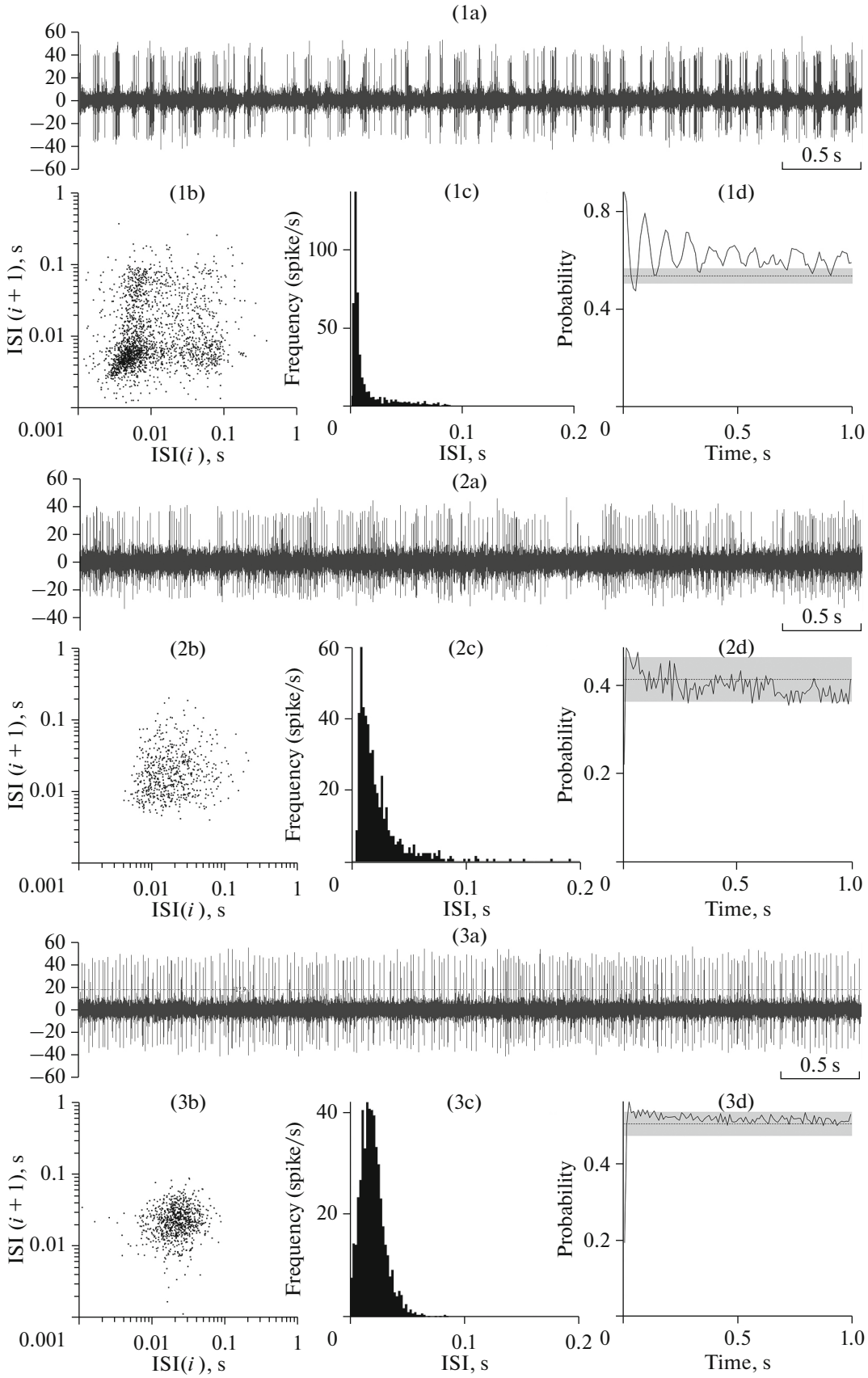

Fig. 2. Examples of (a) activity recording, (b) Poincare maps, (c) histograms of ISIs, and (d) autocorrelogram for different types of STN neurons. 1, bursting neurons; 2, irregular tonic neurons; 3, regular tonic neurons.

ventral STN regions. As is shown in Fig. 3a, tonic neurons were generally located in the ventral part of the nucleus. The lower half of the nucleus concentrated 75% of regular and 72% of irregular tonic neurons. Bursting neurons were distributed uniformly over the STN mass. We should also note that the characteristics of bursting neurons significantly varied along the electrode movement trajectory. The mean AI parameter increased up to 0.65 from 0.53, whereas the mean CV value decreased to 1.06 from 1.32 along the trajectory of the electrode with its deeper insertion into the nucleus. This type of dependence has not been found for tonic neurons.

DISCUSSION

There are no generally accepted methods today for discriminating the spontaneous neuronal activity patterns in the basal ganglia nuclei. Recent studies have shown that there is no single neuronal activity parameter which would be able to evaluate the severity of pathophysiological alterations in the basal ganglia nuclei in PD [20]. At the same time, there are no doubts about the idea that alterations in the activity patterns of the basal ganglia, and, particularly, in the STN, play an important role in the pathophysiology of PD [20, 21]. In fact, many researchers believe that the development of PD symptoms is primarily associated with the increase of bursting activity in the STN [14, 15, 20], including rhythmic activity in the low-frequency and β ranges [17, 18]. Thus, an important task of modern neurophysiology is to identify the typical characteristics of neuronal activity, which would allow us to describe differences between the functioning of the STN in the healthy and pathological conditions.

The early studies which analyzed neuronal activity patterns in the STN contained attempts to apply the methodology developed for assessing bursting activity in thalamic nuclei [13], such as the bursting activity index calculated as the ISI median divided by the mean discharge activity, to identify bursting neurons. In this case, cells were considered bursting if the bursting activity index value exceeded 10, whereas the median value of this index for the STN neuronal population reached 3.3 (compared with the median value of this index reaching 29 for the thalamic nuclei). There were also attempts to visually analyze recordings to distinguish activity patterns [10, 15], and while in the former case, researchers based primarily on the pattern of spike location on the spike train, they used histograms of the ISI distribution and the ISI variability assessment (AI and CV of ISIs) in the latter case. In both cases, researchers distinguished tonic, irregular, and oscillatory (bursting) types of activity, which statistically differed in terms of activity parameters; however, the particular characteristics of the distinguished types substantially diverged between these two studies. Steigerwald et al. made an attempt to specify the boundary criteria for discriminating activity patterns

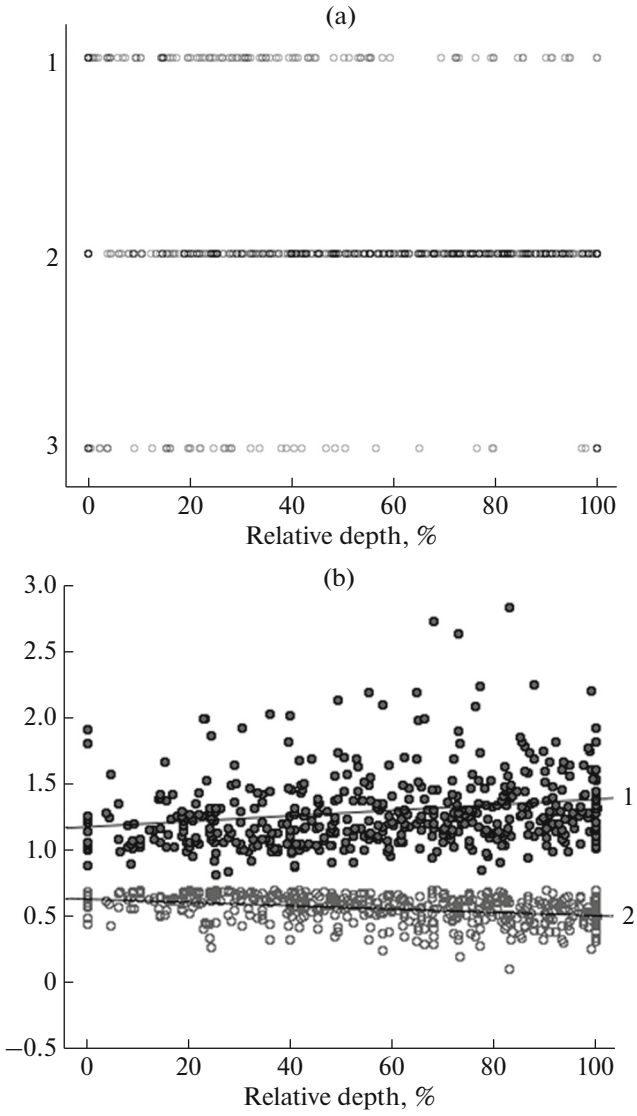

Fig. 3. Changes in neuronal activity along the electrode movement trajectory in the dorsoventral direction: (a) distribution of different types of neurons in the dorsoventral plane relative to the electrode movement trajectory (in % of the STN length from the exitt point to the entry point); 1, irregular tonic neurons; 2, bursting neurons; 3, regular tonic neurons. (b) distribution of the CV values of ISIs (1) and the AI values of ISIs (2) for bursting neurons relative to the electrode movement trajectory.

based on the ISI variability parameters; however, the parameter values for the isolated groups were overlapped and unspecified in any formal way which would give researchers the possibility to exactly reproduce the results of the study [15].

We have used the values of AI and CV of ISIs to develop the method for the formal discrimination of spontaneous neuronal activity patterns in the STN. To calculate the AI, we used the median value of ISIs, not the value of the mode, as Steigerwald et al. [15] used, since the median is more stable in the analysis of dif-

ferent record segments of the same neuron, especially in the case of irregularly discharging cells. In addition, we used nonoverlapping boundary values to distinguish regular and irregular activity patterns, which clearly allowed us to attribute a neuron to a particular group, based on the formal characteristics of its activity.

The study described the characteristics of three types of spontaneous neuronal activity in the STN in patients with PD. According to the data, the bursting type of activity prevails in the nucleus; bursting neurons constitute about 70% of all neurons in the STN. These results agree with the data reported by Steigerwald et al., who used the same approach for the discrimination of different neuronal activity patterns [15]. At the same time, our values of activity parameters for irregular tonic neurons and their representativeness in the nucleus substantially differ from the results reported by the cited study. These differences may be associated with the fact that the authors of the cited study predominantly included neurons with low frequency of activity (on average, 14 spikes/s) into the irregular type, which we, on the contrary, excluded from the consideration because of the insufficient sample of ISIs. Nevertheless, our data on essential differences in the activity parameters of tonic regular and bursting (or oscillating) neurons in PD patients agree with other researchers' conclusions [10, 15]. The increase in the percentage of bursting discharges has also been shown earlier by the destruction of the substantia nigra pars compacta in the rat and monkey [11, 22]. In contrast to these results, the analysis of activity patterns for the STN neurons in healthy monkeys have shown the homogeneity of this structure [23].

The studies of intracellular activity in animals have shown the possibility for switching between the tonic and bursting regimens in the functioning of the STN neurons, which occurs through altering the membrane potential [24]. Thus, the bursting activity of STN neurons in PD patients may result from a deeper hyperpolarization of cells affected by input projections of the "indirect" pathway.

In addition, we have detected neurons oscillating in the β range, and they accounted for almost 6% of bursting neurons. Although these neurons did not differ from other neurons with bursting activity in terms of AI and CV of ISIs, the value of their discharge activity was significantly higher. These results agree with the reports of other researchers [18, 25], who have shown an increased discharge activity of neurons oscillating in the low-frequency and β ranges in patients with PD. In addition, a direct association has been shown between the β activity in STN and the akinetico-rigid manifestations in PD [18].

These results also confirm that the pathological activity in the STN of patients with PD is manifested, apart from the increased discharge frequency, in the transformation of the tonic pattern into the bursting rhythmic activity pattern.

The most important specific feature that we found when analyzing spontaneous neuronal activity of the STN was the heterogeneity in the distribution of different activity patterns along the electrode movement trajectory. Tonic neurons were predominantly localized in the ventral part of the nucleus. We should note that the characteristics of bursting neurons, which were distributed almost uniformly across the STN mass, became closer to the parameter values of tonic neurons with approaching to the ventral boundary of the nucleus. In fact, the population activity of neurons in the dorsolateral part of the nucleus was characterized by a higher level of burstiness, whereas the ventromedial part had a higher level of tonic activity. These results agree with the morphological data that the dorsolateral part of the STN had projections to the motor areas of the cortex, whereas the projections of the ventromedial part were directed to the associative regions [26]. In addition, histological and functional studies with the participation of patients have reported that the decrease in the level of dopamine due to PD was manifested more strongly in the putamen sending projections to the motor part of the STN, whereas pathological alterations in the nucleus caudatus linked to the associative region of the STN were less expressed [27]. Thus, the pathological bursting activity predominantly embraces the "motor" areas of the STN, whereas the associative areas were less susceptible to pathological alterations. Some researchers isolated two separate areas in the posterior part of the STN: the dorsolateral oscillating region and the ventromedial non-oscillating region [26]. According to the data, the boundary between these two regions was distinguished rather conventionally; i.e., the neuronal activity characteristics gradually altered along the microelectrode movement trajectory from the point of entry into the nucleus to the point of exit, without marked transitions.

On the whole, our data confirm heterogeneity in the neuronal organization of the STN in patients with PD. We believe that a differential analysis of discharge activity parameters for individual patterns may be more informative when studying pathophysiological alterations in the STN in PD. The subsequent multiparametric analysis of the activity of the identified patterns will allow us to study associations with the severity of pathological symptoms in patients with PD. The features of the STN neuronal organization and changes in the spontaneous neuronal activity characteristics, apart from the localization of oscillating neurons, may be used in identifying the optimal region of the STN for DBS to alleviate PD symptoms.

Analysis of pathological processes and movement-associated alterations of neuronal activity will be especially important for understanding the PD pathophysiology.

CONCLUSIONS

We have studied the spontaneous activity of STN single units in patients with PD. In the course of the study, we have developed a formal method based on the AI and CV values for ISIs, which allowed us to distinguish three types of spontaneous activity for the STN neurons. It has been shown that bursting neurons account for about 70% of the total STN neuronal population. We have found heterogeneity in the localization of neurons along the microelectrode trajectory: tonic neurons were predominantly localized in the STN dorsal regions, whereas bursting neurons were more uniformly distributed across the nucleus, and their characteristics changed for more tonic ones. Thus, we have confirmed the presence of heterogeneity in the neuronal organization of the STN in patients with PD.

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