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CORRELATION OF EXCITATORY AND DEPRESSIVE SYNAPTIC PROCESSES IN SPINAL CORD MOTONEURONS IN HYPOCALCEMIA DEVELOPMENT DYNAMICS IN PARATHYROIDECTOMIZED RATS

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Abstract

Bilateral parathyroidectomy was conducted in experimental animals, and after 3-7 and 21-22 days an isolated spinal cord was obtained by its transection at T2-T3 level under novocaine and immobilization by ditillinum. Registration of activity from motoneurons of the spinal cord L4-L5 segments to 1-second high-frequency stimulation of flexor (n. Gastrocnemius, G) and extensor (n. Peroneus communis, P) hind limb nerves was performed. Tetanic and posttetanic potentiation and depression were recorded. The analysis of post-stimulus activity was produced by on-line selection and program analysis of the spikes. The average peri-event time histogram of the interspike intervals, cumulative histograms of spikes number and average frequency histograms were used. Overall, 295 neurons were recorded. Background activity of the flexor motoneurons decreased by the 3rd day and was growing progressively since days 4-5 (up to 1.5 times), reached 1.1-fold underestimation by day 22, while those of the extensors, growing by the 4th day, reduced to the same value at day 22. At 50 Hz high-frequency stimulation of the nerve G only on day 22 tetanic potentiation of motoneurons approached the norm, while the tetanic potentiation to 100 Hz in all the days of testing was above norm, progressively growing up to 4.7-fold exceeding. In response to 50 Hz the high-frequency stimulation of P nerve, starting from the 7th day tetanic potentiation of motoneurons increased up to 1.6-fold excess of norm, while to 100 Hz already at the 3rd day it was observed to exceed the norm progressively growing by the 22nd day, likewise the case of nerve G. The tetanic depression of motoneurons to 50 Hz high-frequency stimulation of nerve G, increasing from day 4 to 21 reached 2.3-fold excess of norm; then, at 100 Hz already from the 4th to the 7th day twice exceeding the norm, and at the 21st day it dropped up to 1.5 times. The tetanic depression of motoneurons to 50 Hz high-frequency stimulation of P nerve, already at the 4th and until the 21st day reached a 1.5-fold excess, at the 22nd day approached the norm and in response to 100 Hz, being at the 4th day 3 times higher than norm, decreased up to twofold exceeding of norm at the 7th day, reaching the level of norm at the 22nd day. In general, with the pathology development there was an abrupt increase of excitatory and depressor effects, but by the end of tests only depressor effects reached the norm.

The posttetanic potentiation and posttetanic depression of motoneurons to high-frequency stimulation of both nerves, likewise the norm, accompanied tetanic potentiation in all the terms. The tetanic depression of motoneurons to high-frequency stimulation of G nerve changed into the posttetanic potentiation in the early days and later on into posttetanic depression; the tetanic depression of nerve P equally turned in both terms, while in norm tetanic depression from both nerves changed into posttetanic potentiation in response to 100 Hz and into the posttetanic depression under 50 Hz.

Keywords: *parathyroidectomy, extensor and flexor branches of the sciatic nerve, spike activity of single spinal motoneurons.*

Introduction

It is known that Ca^{2+} acts as a universal signal responsible for the control and regulation of the wide range of neuronal functions, including growth of processes, synaptogenesis, synaptic transmission, plasticity and survival, and their dysregulation leads to synaptic dysfunction, plasticity disturbance, development of neuropathology and degenerative diseases [*Mattson M., 2007*]. In addition, the Ca^{2+} endoplasmic reticulum serves many functions, including modulation of synaptic inputs and plasticity [*Fujii S. et al., 2000*]. It is also known that neuronal activity is accompanied by an increased concentration of cytosolic Ca^{2+} to associate with calmodulin as a second messenger mediating the physiological responses of neurons to

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chemical and electrical stimulation. In normal physiological activity the intracellular Ca^{2+} level increases briefly and has no side effects on neurons. However, at aging and various disease processes the ability of neurons to control the level of Ca^{2+} is broken [*Mattson M., 2007*].

Discovery of the Ca^{2+} ability to act as an external ligand, together with the molecular cloning of its surface cellular receptors (e.g., Calcium Sensing Receptor) showed that Ca^{2+} is a primary and important extracellular messenger [*Bouschet T., Henley J., 2005*]. It was also shown that neurons communicate to each other through accumulation, release and subsequent action of the mediator, while the entrance of Ca^{2+} through the potential- and ligand-dependent channels in the plasma membrane was a major trigger for the release of neurotransmitter from presynaptic terminals [*Yuste R. et al., 2000; Burnashev N., Rozov A., 2005*]. The relationship between the input of Ca^{2+} and the release of neurotransmitter was shown to be complicated and complex; nevertheless, the decrease of Ca^{2+} entry led to disruption of neurotransmitter release [*Feng Z., Durand D., 2006*]. Therefore, a disturbance of Ca^{2+} homeostasis might disrupt the normal functioning of neurons. In turn, for example, in case of hippocampus it was shown that low levels of Ca^{2+} in combination with high K^+ levels promoted the generation of stable long-term epileptiform spike activity [*Feng Z., Durand D., 2006*]. Particularly, under conditions of vestibular neurons deprivation, the authors showed an increase of pacemaker activity responsible for the recovery of spontaneous activity. It was also found that blockade of synaptic transmission epileptiform activity might be caused by nonsynaptic mechanism [*Feng Z., Durand D., 2006*]. During interaction of neurons Ca^{2+} ions, which constantly modulate the degree of synaptic communication, are the most important factor in the release of neurotransmitter. Basically, the release of neurotransmitter is under control of N and P/Q Ca^{2+} channels. Although the relationship between the input of Ca^{2+} and the release of a mediator is rather complex, lowering of Ca^{2+} level in the organism leads to disruption of neurotransmitter release, and consequently the normal functioning of neurons [*Miller R., 1998*].

The parathyroid hormone (PTH), a major regulator of specific calcium-phosphorus metabolism in the body, maintains a stable level of extracellular Ca^{2+} by stimulating its reabsorption in the kidneys, intestinal absorption, release from the bones. Therefore, PTH levels *via* the negative feedback balance the extracellular Ca^{2+} [*Bouschet T., Henley J., 2005*]. Due to lowering of PTH synthesis hypocalcemia leads to a variety of neurological symptoms, in particular, tetany syndrome, often leading to death [*Davis F., Schauf C., 1976*]. By the example of ventromedial nucleus of the hypothalamus, one of the sites of PTH calciotropic function, inhibition of neuronal activity through postsynaptic mechanism mediated by PTH receptors was shown [*Matsui H. et al., 1995*].

From the clinical experience we know that symptoms of motor area disorders (parathyreoprivous tetany) are on the leading place in the entire picture of hypoparathyroidism. As early as in 1984, we used a method of spinal cord (SC) reflexes testing in animals with parathyreoprivous tetany to demonstrate partial or complete loss of monosynaptic reflex responses with the simultaneous increase of polysynaptic responses, increase of the speed in excitation conduction outside the spinal monosynaptic arc and deceleration of intraspinal conduction in synaptic link as a response to a single stimulation, increase in reproducibility of the reflex responses during rhythmic stimulation, relaxation of posttetanic enhancement of reflexes and shortening in recovery time of motoneurons pool excitability [*Khudaverdyan D., 1984*]. Our research established that the causes of parathyreoprivous movement disorders include those occurring in various parts of the CNS related to the control and triggering of motor reactions, and the pathological processes at the level of the SC represent the crucial link, as along with the increased excitability of the moto- and interneurons the primary importance gain violations in the system of inhibitory mechanisms, the weakening of all types of segmental inhibition, which is the basis for non-regulated spreading of excitation in the SC with its output to the periphery and the triggering of convulsive reactions [*Khudaverdyan D., 1984*].

It is also known that modulating effects of PTH on neuron functions occur through regulation of the intracellular level of Ca^{2+}, cAMP and sGMP. PTH is directly or indirectly involved in activation of adenylate cyclase and cAMP synthesis, cell membrane permeability, nervous electrogenesis, muscular and glandular tissues, synaptic transmission and the mechanism of muscle contraction [*Khudaverdyan D., Ter-Markosyan A., 2000*].

Thus, the study on neurons functional activity at disorders of Ca^{2+} homeostasis caused by disturbance of PTH synthesis should be considered extremely important. Despite the numerous research works in the field of hypocalcemia, there remain completely unresolved mechanisms of abrupt increase in neuronal excitability after parathyroidectomy (PTX), which appear both in the background, and in the evoked activity. Moreover, there is a need for a detailed study on the dynamics of these changes not only in the early, but also in later periods after PTX, as well as the neural mechanisms of mentioned segmental abnormalities. Probably, the increase of frequency might be related to onset of such pacemaker endogenous activity, beyond the possible synaptic response ability, with a glance of neurons electric constants. These data make necessary further investigation on the role of impaired Ca^{2+} homeostasis and PTH in cellular mechanisms of identified systemic disorders formation at tetany. Finally, the study on mentioned reflexes and neural mechanisms of their formation in conditions of latent tetany (chronic hypoparathyroidism) deserves special consideration; this is important in terms of the applied clinical importance. In connection with the foregoing, the need is evident in extra- and intracellular studies on the functional state of SC neurons in tetany. These studies, together with the study on the effects of PTH and Ca^{2+} to the activity of spinal neurons, will allow, on the one hand, to assess the role of PTH and impaired Ca^{2+}-phosphorus metabolism in the CNS and, on the other hand, to reveal the cellular mechanisms of segmental locomotor disorders in tetany.

Thus, the important role of Ca^{2+} homeostasis and its regulatory mechanisms to ensure the normal functioning of neurons makes paramount the research on causes of functioning disruption of neurons in Ca^{2+} homeostasis. This applies particularly to SC neurons, the functional state violation of which might be a determining factor in development of the parathyroprivous tetany syndrome. In the present work further study on the effect of parathyroid glands absence in the functional state of SC motoneurons (MNs) was undertaken.

MATERIALS AND METHODS

Experiments were performed in male Albino rats (250 ± 30 *g*): intact (n = 13) and subject to bilateral PTX (n = 12). All procedures were performed according to the "Rules for the care of laboratory animals" (NIH publication No. 85-23, revised in 1985), as well as specific guidance provided by Animal Care Committee and the National Health Service. In 3-7 and 21-22 days after PTX and fixation in a stereotaxic apparatus, to achieve isolated SC the rats were immobilized with 1% ditillinum (25 *mg/kg, i.p*), and under artificial respiration and novocaine the SC was transected at T2-T3. After dorsal laminectomy of the SC lumbosacral section the stereotactically oriented [*Paxinos G., Watson C., 2005*] glass microelectrodes with the tip diameter of 1 *mm* containing 2 M NaCl solution were inserted into the anterior horn of the gray matter of the lumbar segments (L4-L5) in the region of SC MNs (VIII-IX plates by Rexed) for extracellular recording of background and evoked spike activity of single MNs in response to high-frequency stimulation (HFS) (0.05 *ms*, 0.8-1.6 *mA*, 50 and 100 *Hz* for 1 *sec*) of hind limbs ipsilateral extensor (*n. Peroneus communis* - P) and flexor (*n. Gastrocnemius* - G) nerves by bipolar silver electrodes. Overall, 295 SC neurons were recorded. To evaluate the excitatory and depressive post-stimulus effects, the tetanic potentiation (TP) and depression (TD) followed by posttetanic manifestations in the form of posttetanic potentiation (PTP) and depression (PTD) were used. Analysis of early and late post-stimulus manifestations of activity was carried out in on-line selection mode and software analysis of spikes. We constructed complex averaged and summarized peri-event time histogram (PETH), cumulative histograms of spikes with difference curve and frequency histogram calculating the average frequency of spikes. On average, during one registration up to 10-15 post-stimulus tests were performed. The analysis of data was produced by the specially developed algorithm. Software analysis provided the possibility to isolate artifacts during tetanization, which allowed mostly consider it as strictly constant, in contrast to the less stable posttetanic excitatory and inhibitory effects. To determine the statistical significance of differences in interspike intervals duration before and after the stimulus, a nonparametric test check of two independent samples – two-sample Wilcoxon-Mann-Whitney's test – was used. Since the number of recorded spikes were quite large (up to several hundreds of spikes in 20-second intervals after the stimulus), we used a variation of this test, which takes into account its asymptotic normality – z-test. The comparison of critical and tabulated values of the normal distribution at a significance level of 0.05, 0.01 and 0.001 (for different trials) showed that as a result of HFS for most samples of neuronal spiking activity there was a statistically significant change with a significance level of at least 0.05.

RESULTS

Overall, 295 SC neurons were recorded: 242 neurons after PTX and 53 neurons in the norm.

According to PETH, at 50 *Hz* HFS of G nerve on day 22 the TP approached norm (Figure 1 A and B), while at 100 *Hz* HFS on all the days of testing the TP was higher than in norm, progressively growing up to 4.7-fold of its excess (Figure 2 A, B). At 50 *Hz* HFS of P nerve, on the contrary, starting from the 7th day TP increased up to 1.6-fold above the norm (Figure 3, A, B), while at 100 *Hz* HFS the TP already from the 3rd day exceeded the norm, growing progressively at the 22nd day, likewise the case of nerve G, up to 4.8-fold of its excess (Figure 4 A, B). The TD at 50 *Hz* HFS of G nerve was increasing from the 4th to 21st day up to 2.3-fold over norm (Figure 1 C, D), while at 100 *Hz* HFS it was twice exceeding the norm already from the 4th to 7th day and at the 21st day subsided up to 1.5 times (Figure 2 C, D). At 50 *Hz* HFS the TD already since the 4th day and at the 21st day was reaching 1.5-fold of its excess, at the 22nd day it approached the norm (Figure 3 C, D), whereas at 100 *Hz* HFS it was 3 times higher than norm at the 4th day, then reduced up to twofold exceeding of norm at day 7 and reached the norm by the 22nd day (Figure 4 C, D).

According to the frequency analysis of correlation between the pre- and poststimulus displays of excitatory and inhibitory activity, the following values were obtained and presented in Figures 5-11 for 100 *Hz* HFS as the most effective one. In Figure 5 in the norm, likewise the rest of figures, specific activity rasters of SC MNs to stimulation of G and P nerves were presented in the form of TP (A, C, respectively) and TD (B, D, respectively), together with examples of the detailed analysis for one of the randomly selected examples of activities marked with an asterisk. The same is in Figures 6-11 by the example of similar tetanic effects in conditions of postoperative hypoparathyroidism at days 3-7 and 21. Overall, the TP at 50 *Hz* HFS of the G nerve, being equal to the norm by the 3rd day, on days 5 and 7 was below and by the 4th and 21st day – slightly above the norm; only at the 21st day TP was about twofold higher than norm. The TP at 100 *Hz* only at the 7th day increased progressively up to 4.5-fold exceeding on day 22. The TD at 50 *Hz* HFS was below the norm on all days, except the 4th day, when it exceeded the norm 2.5 times. At 100 *Hz* HFS, the TD exceeded norm only from the 4th to 7th day reaching the maximum in the range of almost 4-fold of its excess on the 5th day and decreased by the end of the tests. The TP to 50 *Hz* HFS of the nerve P, growing from day 7 reached a 2.3-fold excess by the 22nd day, while at 100 *Hz* HFS since the 3rd day it was growing very rapidly, saltatory and at the 22 day reached a 7-fold excess of the norm. The TD at 50 *Hz* HFS of the nerve P reached the norm only at the 4th day, while in response to 100 *Hz* there was a 2-fold excess.

As for posttetanic effects, compared with the level of background activity, at 50 and 100 *Hz* the HFS of nerve G, for all days of testing, likewise the norm, TP was accompanied by PTP, while TD at 50 *Hz* was also accompanied by PTP, except for days 3, 7 and 21, when PTD was registered as in norm, whereas at 100 *Hz* the PTP was recorded only at the 3rd and 5th days as is norm, but in other days – PTD. At 50 and 100 *Hz* HFS of the P nerve TP changed only to PTP as in the norm, while the TD in response to 50 and 100 *Hz* HFS was accompanied by PTP (on days 3, 5 and 22) and by PTD (in other terms), while in the norm at 50 *Hz* HFS we recorded PTD and at 100 *Hz* PTP was registered.

DISCUSSION

The results of recent investigations in the field of hypoparathyroidism and associated pathological changes in the nervous, muscular, and skeletal systems are of interest. As noted above, the term hypoparathyroidism reflects the group of diseases, in which the levels of extracellular Ca^{2+} cannot be maintained in the normal range, because of the relative or absolute deficiency of PTH leading to hypocalcemia and hyperphosphatemia that results mainly in neuromuscular dysfunction. The assessment of neurological diseases in patients with hypoparathyroidism is also of interest. The clinical symptoms in patients with hypoparathyroidism during the normocalcemic period were assessed with the attempt to establish its etiology (electrolyte imbalance, organic CNS injury combined with tetany and epilepsy). The following conclusions were drawn:

Hypoparathyroidism leads to functional and morphological changes in the CNS;

Restoring the metabolic balance through introduction of Ca^{2+} and active vitamin D formulations can withdraw the need for anti-epileptic treatment;

The focus of calcification in the CNS is apparently associated with the duration of hypoparathyroidism;

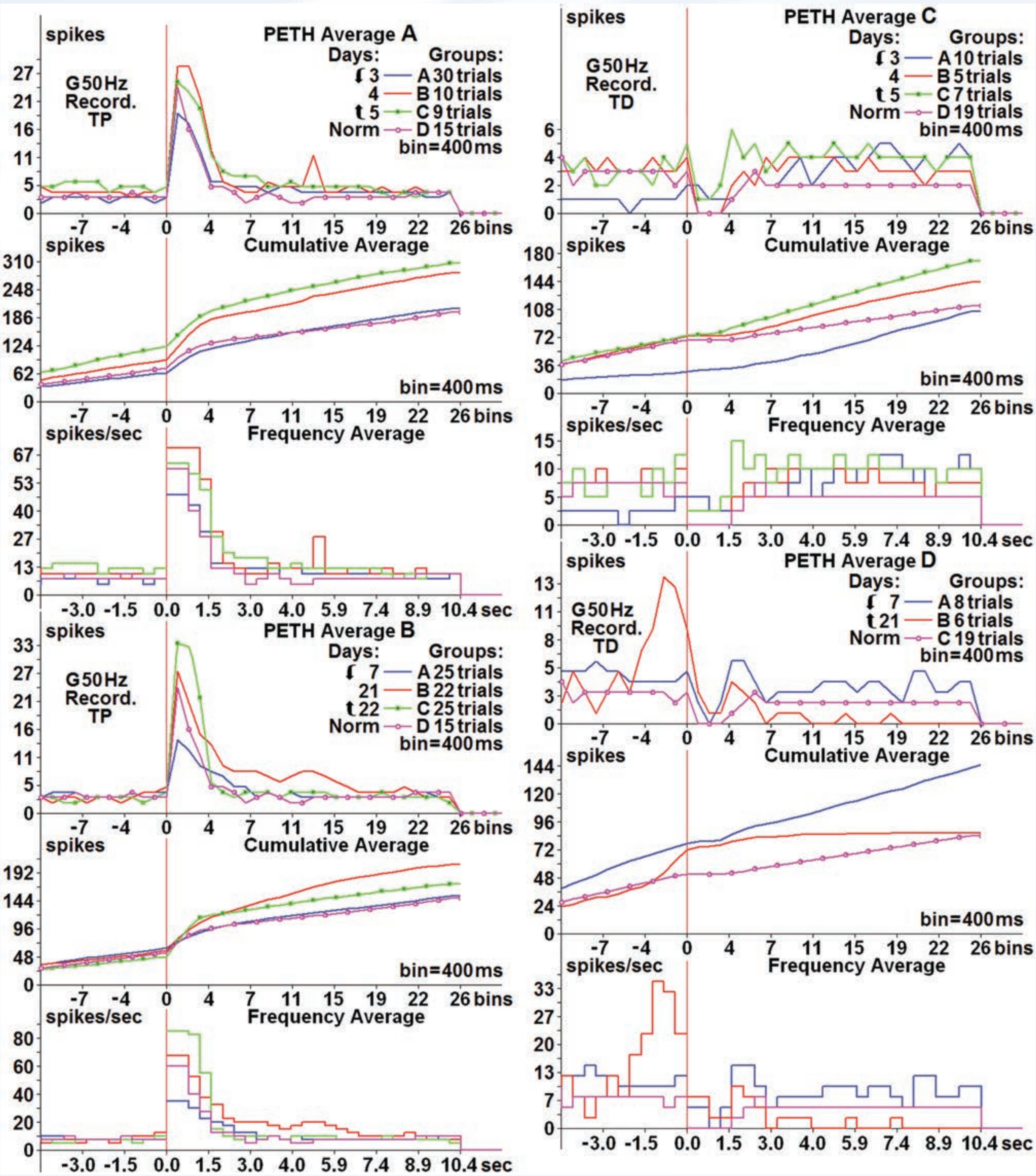

FIGURE **1.** *Averaged peri-event time histograms (PETH Average), cumulative histograms (Cumulative Average) and frequency histograms (Frequency Average) of excitatory (A, B) and depressor (C, D) post-stimulus manifestations of the activity of spinal cord motoneurons to 50 Hz HFS of nerve G, in 3-5 (A, C) and 7, 21-22 (B, D) days after PTX in control and norm (Groups A-C and D, respectively), for A-C (Groups A, B, and C, respectively) and for D. Notation here and in the rest of figures: Record. – Recording.*

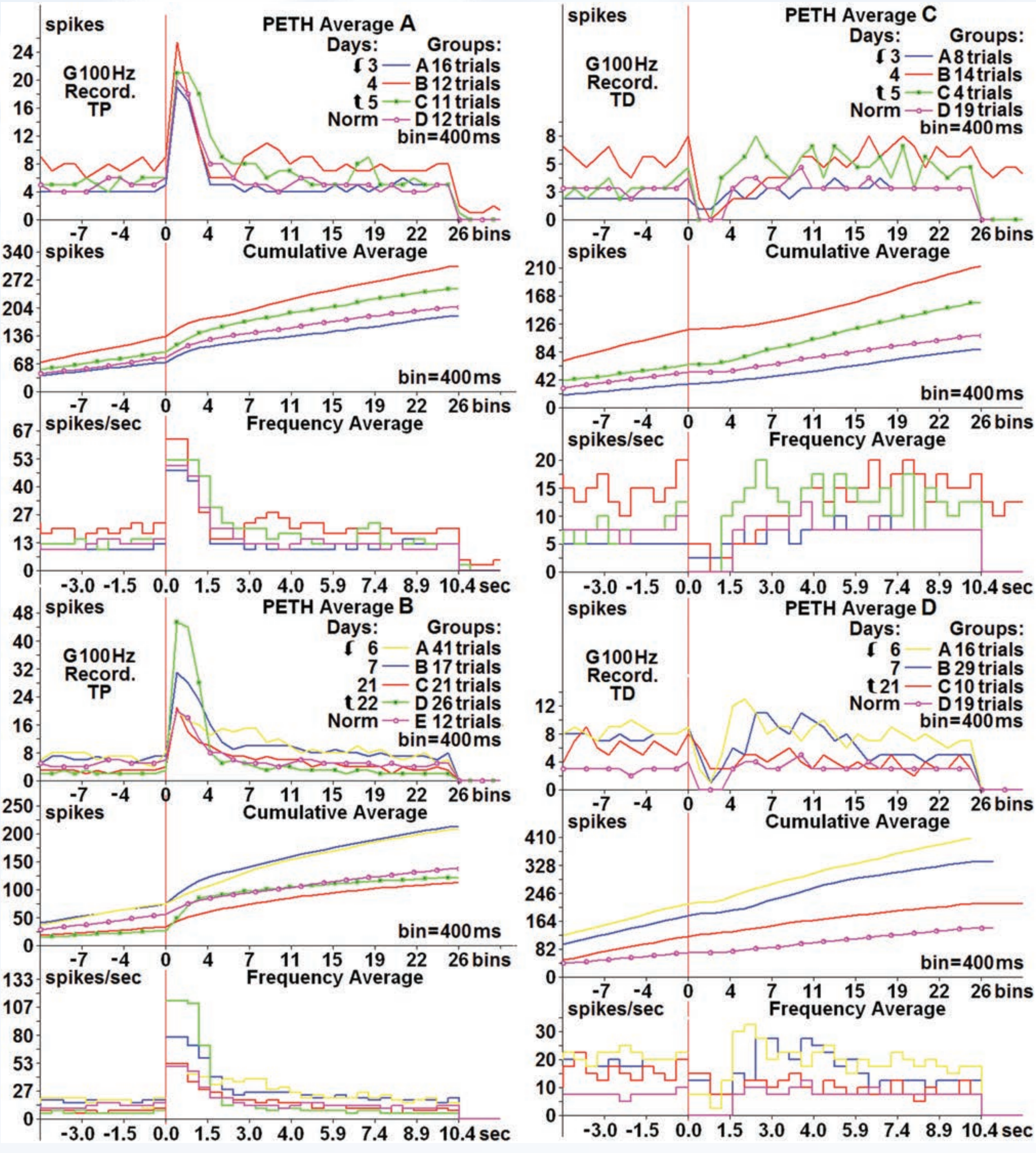

***Figure* 2.** *Averaged peri-event time histograms (PETH Average), cumulative histograms (Cumulative Average) and frequency histograms (Frequency Average) of excitatory (A, B) and depressor (C, D) post-stimulus manifestations of the activity of spinal cord motoneurons to 100 Hz HFS of nerve G, in 3-5 (A, C) and 6, 7, 21-22(B) and 6, 7, 21(D) days after PTX in control and norm for A-C (Groups A-C and D, respectively), for B (Groups A-D, and E, respectively) and for D (Groups A-C and D, respectively).*

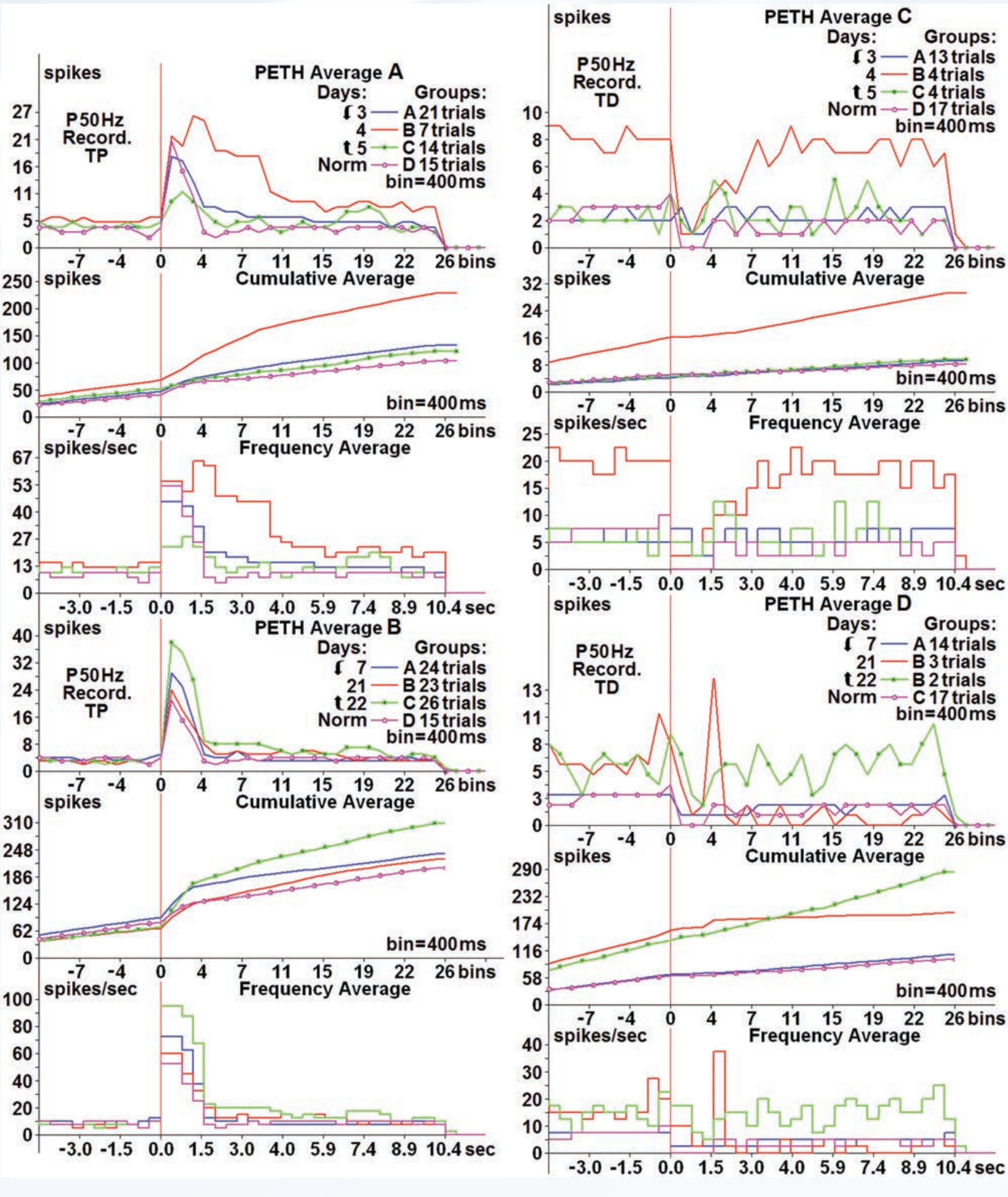

Figure 3. *Averaged peri-event time histograms (PETH Average), cumulative histograms (Cumulative Average) histograms and frequency histograms (Frequency Average) of excitatory (A, B) and depressor (C, D) post-stimulus manifestations of the activity of spinal cord motoneurons to 50 Hz HFS of nerve P, in 3-5 (A, C) and 7, 21-22 (B, D) days after PTX in control and norm for A-C (Groups A-C and D, respectively).*

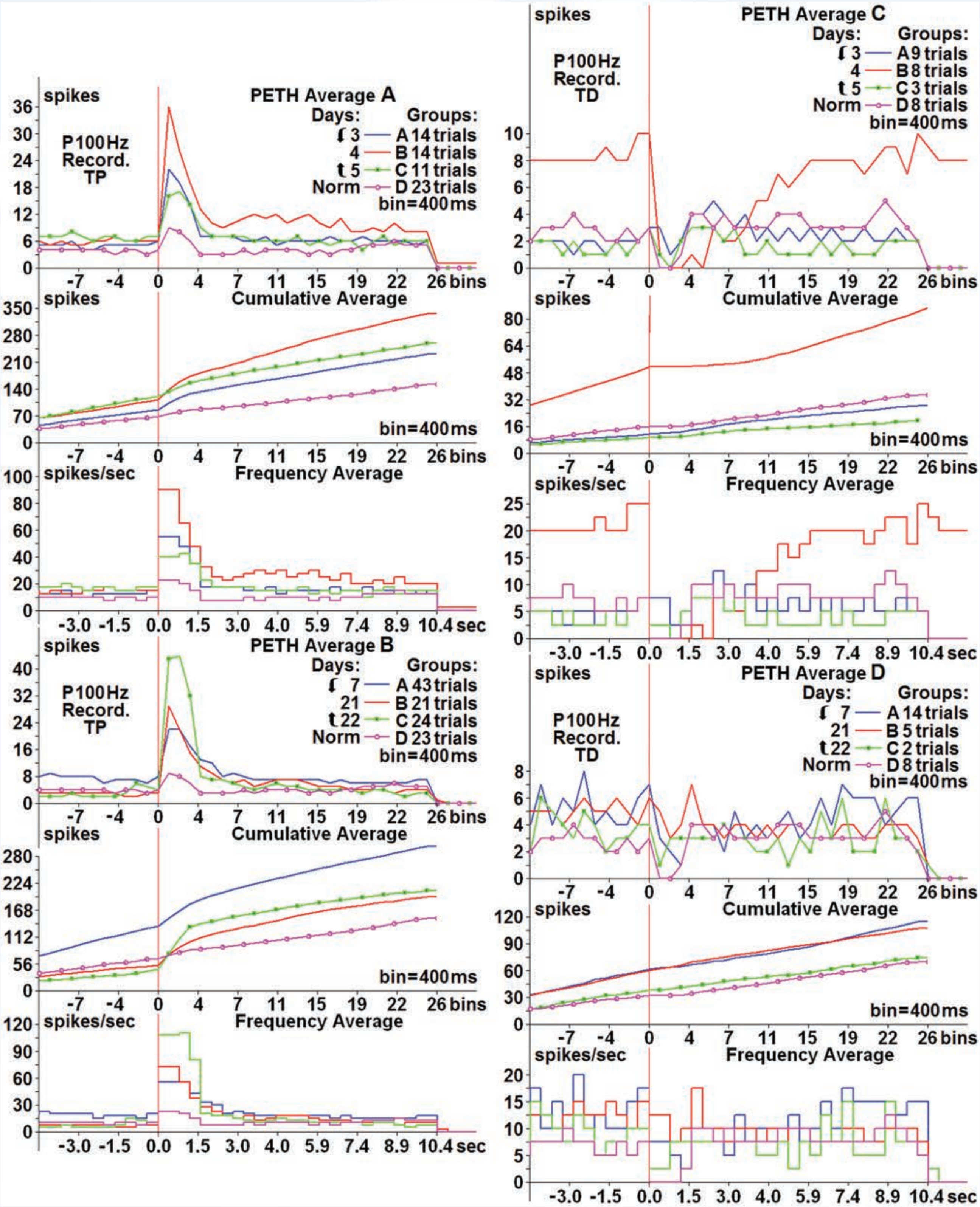

***Figure* 4.** *Averaged peri-event time histograms (PETH Average), cumulative histograms (Cumulative Average) and frequency histograms (Frequency Average) of excitatory (A, B) and depressor (C, D) post-stimulus manifestations of the activity of spinal cord motoneurons to 100 Hz HFS of nerve P, in 3-5 (A, C) and 7, 21-22 (B, D) days after PTX in control and norm for A-C (Groups A-C and D, respectively).*

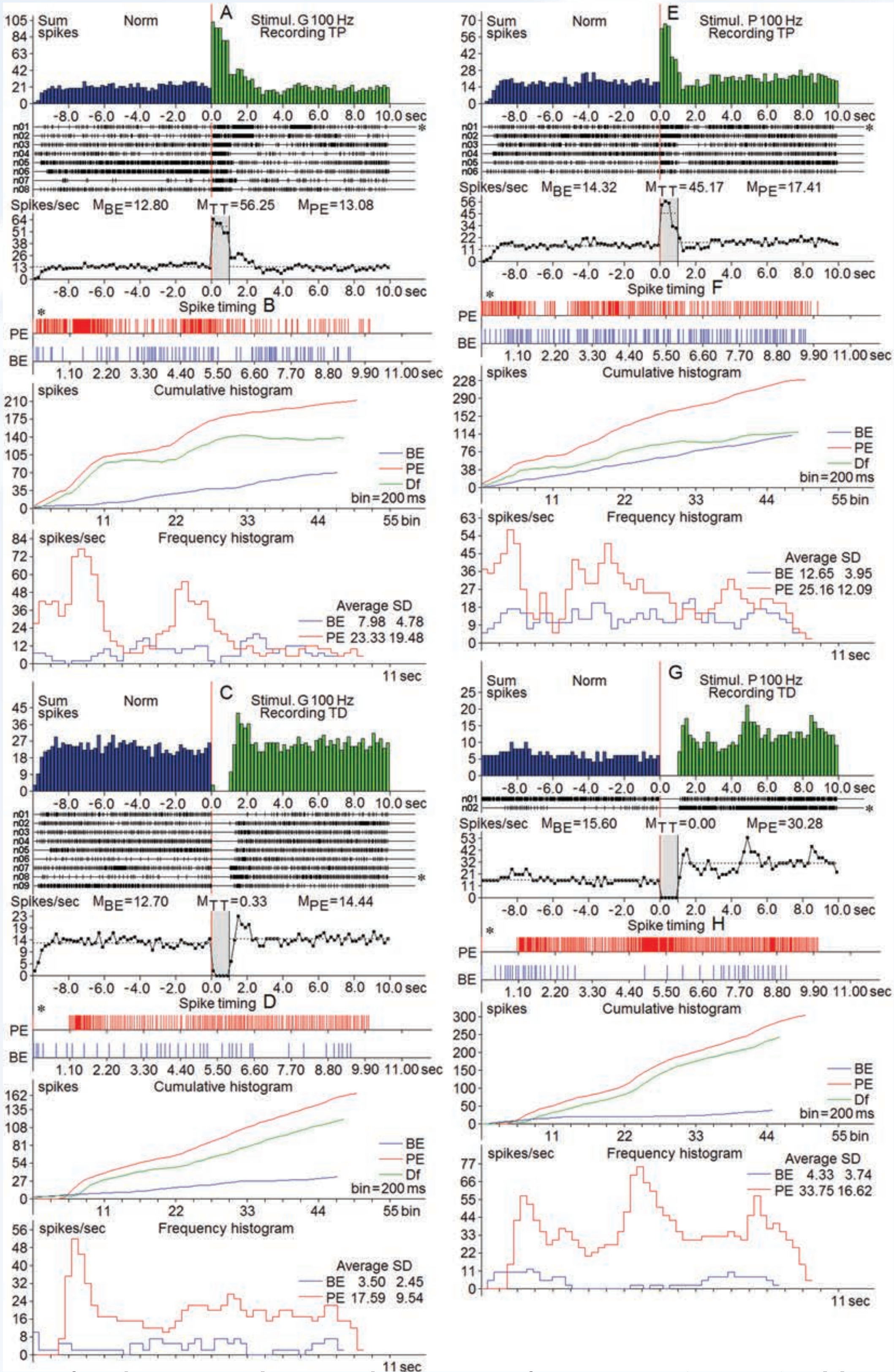

***Figure* 5.** *A-H – from the top pre- and post-stimulus histograms of sum excitatory (A, B, E, F) and depressor (C, D, G, H) displays of spike activity in real time (20 sec before and after stimulation) of single spinal cord moto-neurons in norm evoked by 100 Hz HFS of nerves G (A-D) and P (E-H). Here and in the rest of figures: from the bottom on A, C, E, G – frequency spikes charts with averaged values for the time periods before stimulation (BE – before event), at the time of tetanization (TT – time tetanization) and after stimulation (PE – post event); in B, D, F, H: a detailed analysis of spike activity of one of the randomly selected neuron (indicated by an asterisk on corresponding raster). The rest of notations are presented in the figure.*

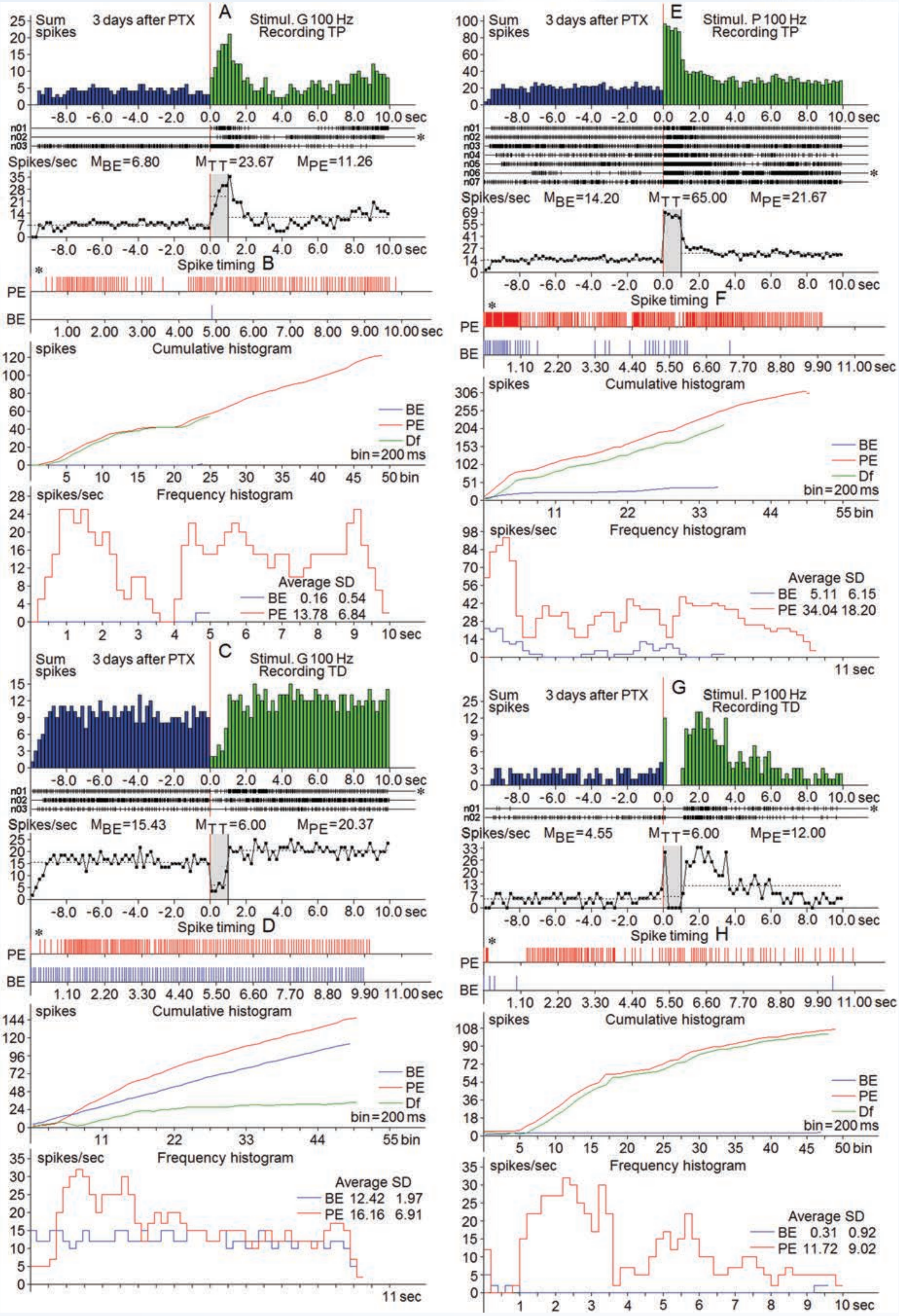

***Figure* 6.** *A-H – from the top pre- and post-stimulus histograms of sum excitatory (A, B, E, F) and depressor (C, D, G, H) displays of spike activity in real time (20 sec before and after stimulation) of single spinal cord motoneurons at the 3rd day after PTX, evoked by 100 Hz HFS of nerves G (A-D) and P (E-H).*

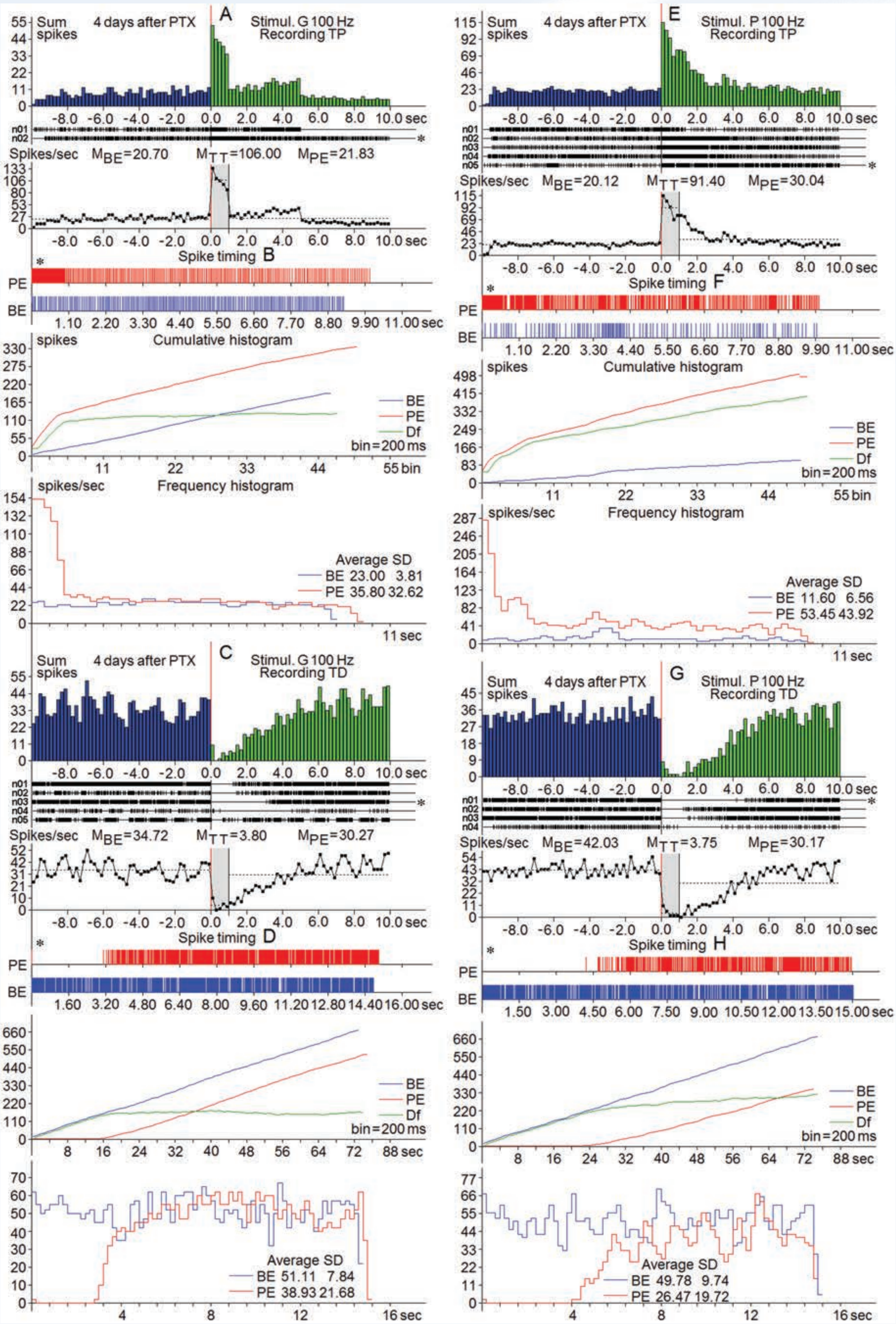

FIGURE **7.** *A-H – from the top pre- and post-stimulus histograms of sum excitatory (A, B, E, F) and depressor (C, D, G, H) displays of spike activity in real time (20 seconds before and after stimulation) of single spinal cord motoneurons at the 4th day after PTX, evoked by 100 Hz HFS of nerves G (A-D) and P (E-H).*

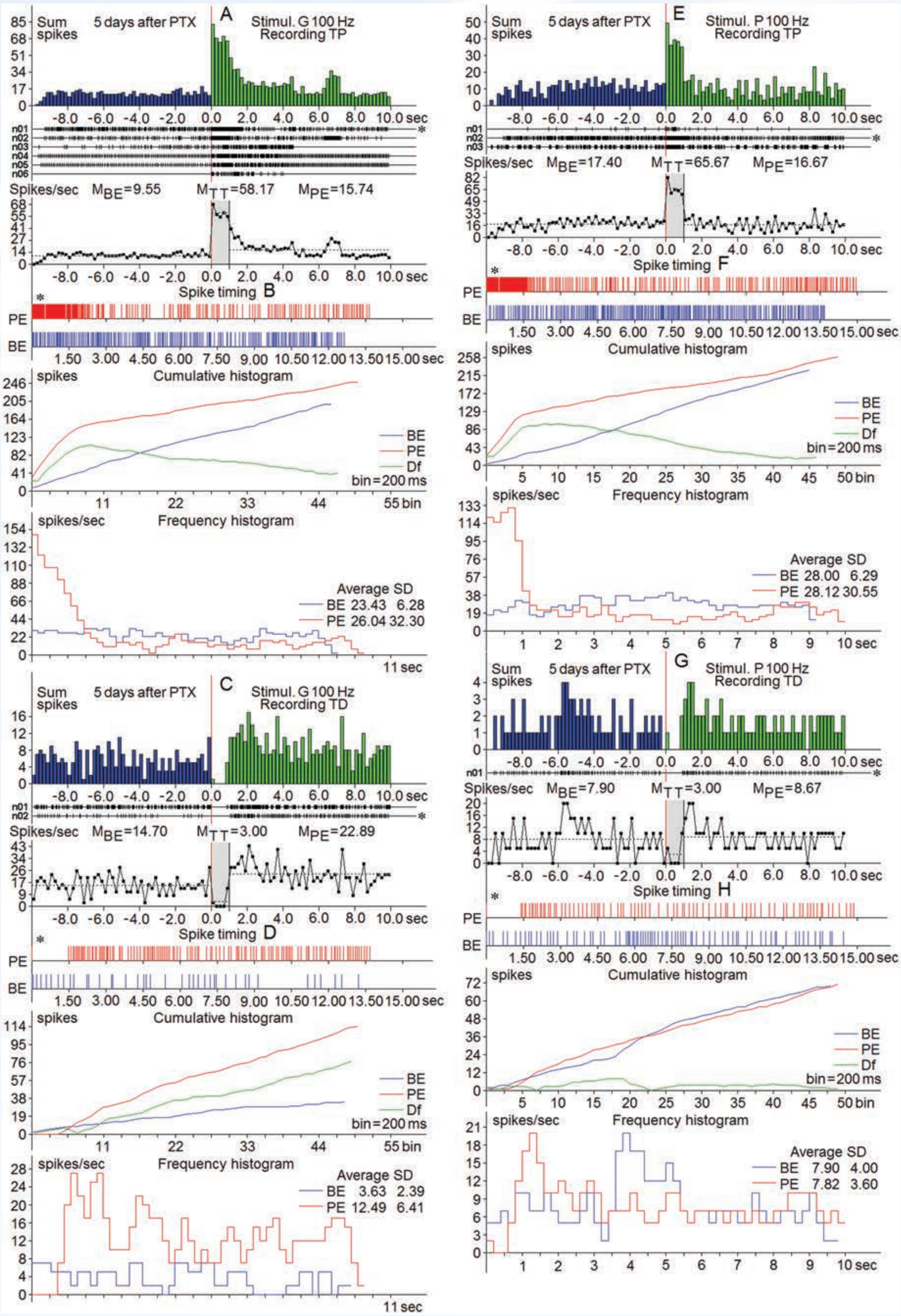

***Figure* 8.** *A-H – from the top pre- and post-stimulus histograms of sum excitatory (A, B, E, F) and depressor (C, D, G, H) displays of spike activity in real time (20 sec before and after stimulation) of single spinal cord motoneurons at the 5th day after PTX, evoked by 100 Hz HFS of nerves G (A-D) and P (E-H).*

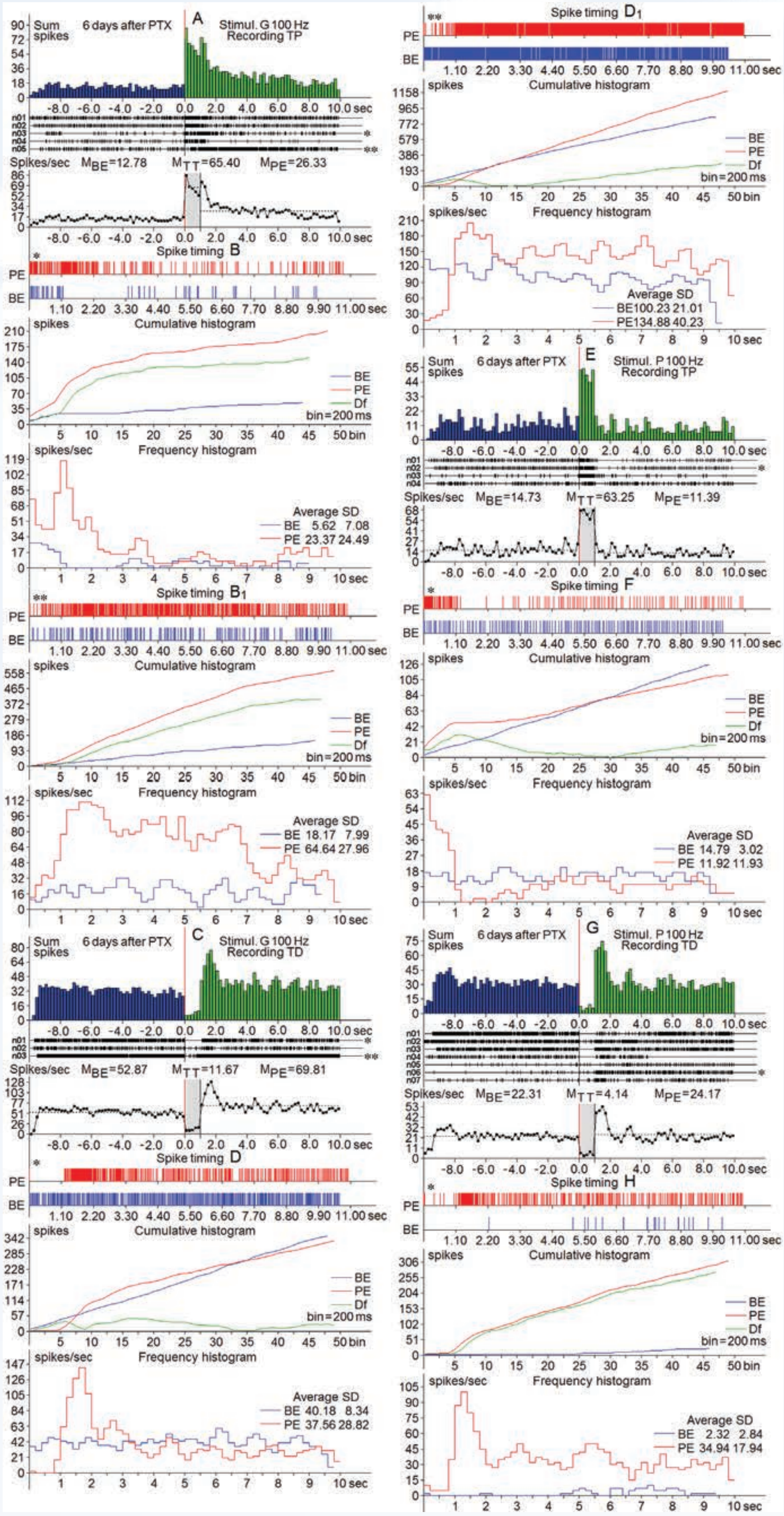

***Figure* 9.** *A-H – from the top pre- and post-stimulus histograms of sum excitatory (A, B, E, F) and depressor (C, D, G, H) displays of spike activity in real time (20 sec before and after stimulation) of single spinal cord motoneurons at the 6th day after PTX, evoked by 100 Hz HFS of nerves G (A-D) and P (E-H).*

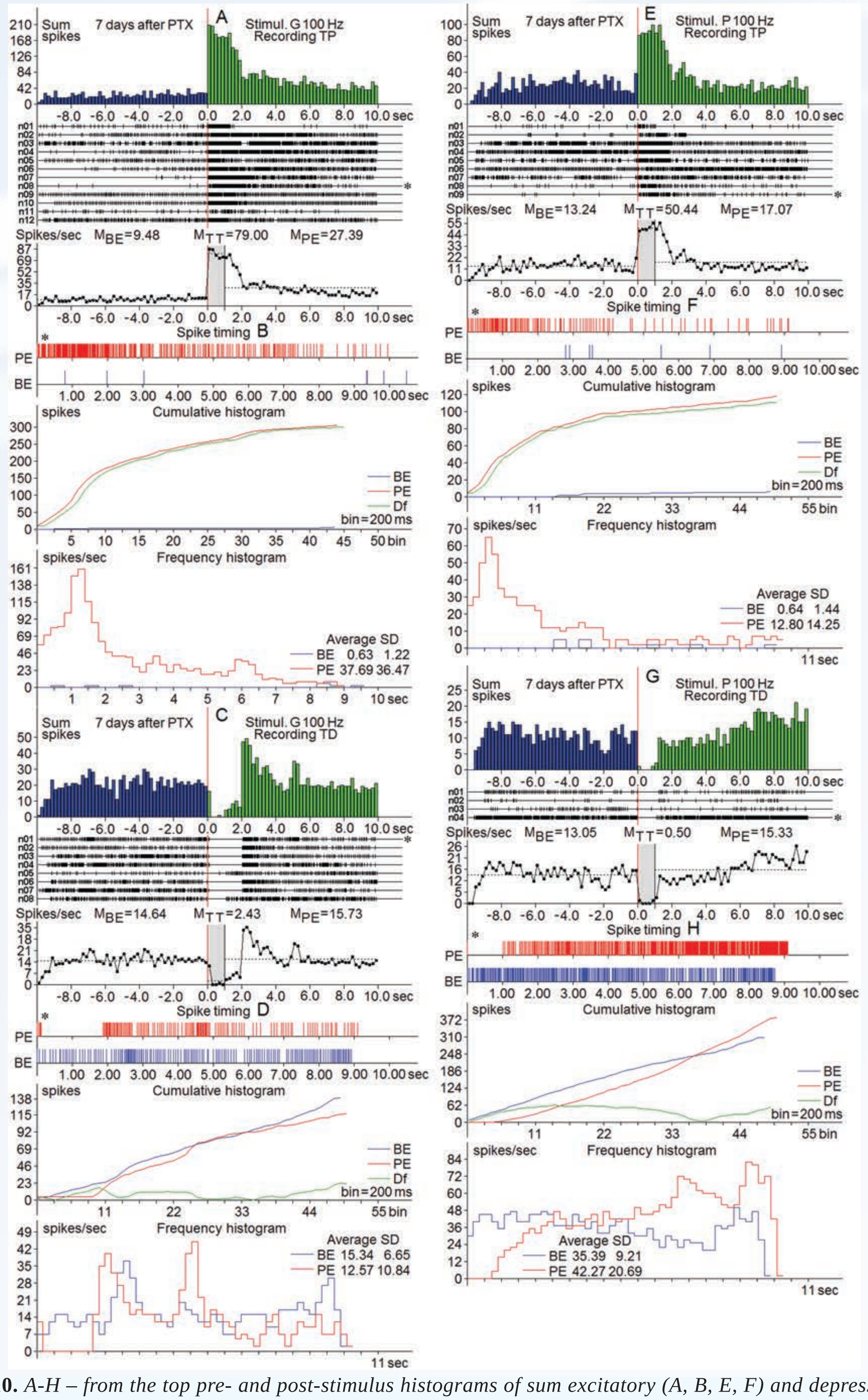

***Figure* 10.** *A-H – from the top pre- and post-stimulus histograms of sum excitatory (A, B, E, F) and depressor (C, D, G, H) displays of spike activity in real time (20 sec before and after stimulation) of single spinal cord motoneurons at the 7th day after PTX, evoked by 100 Hz HFS of nerves G (A-D) and P (E-H).*

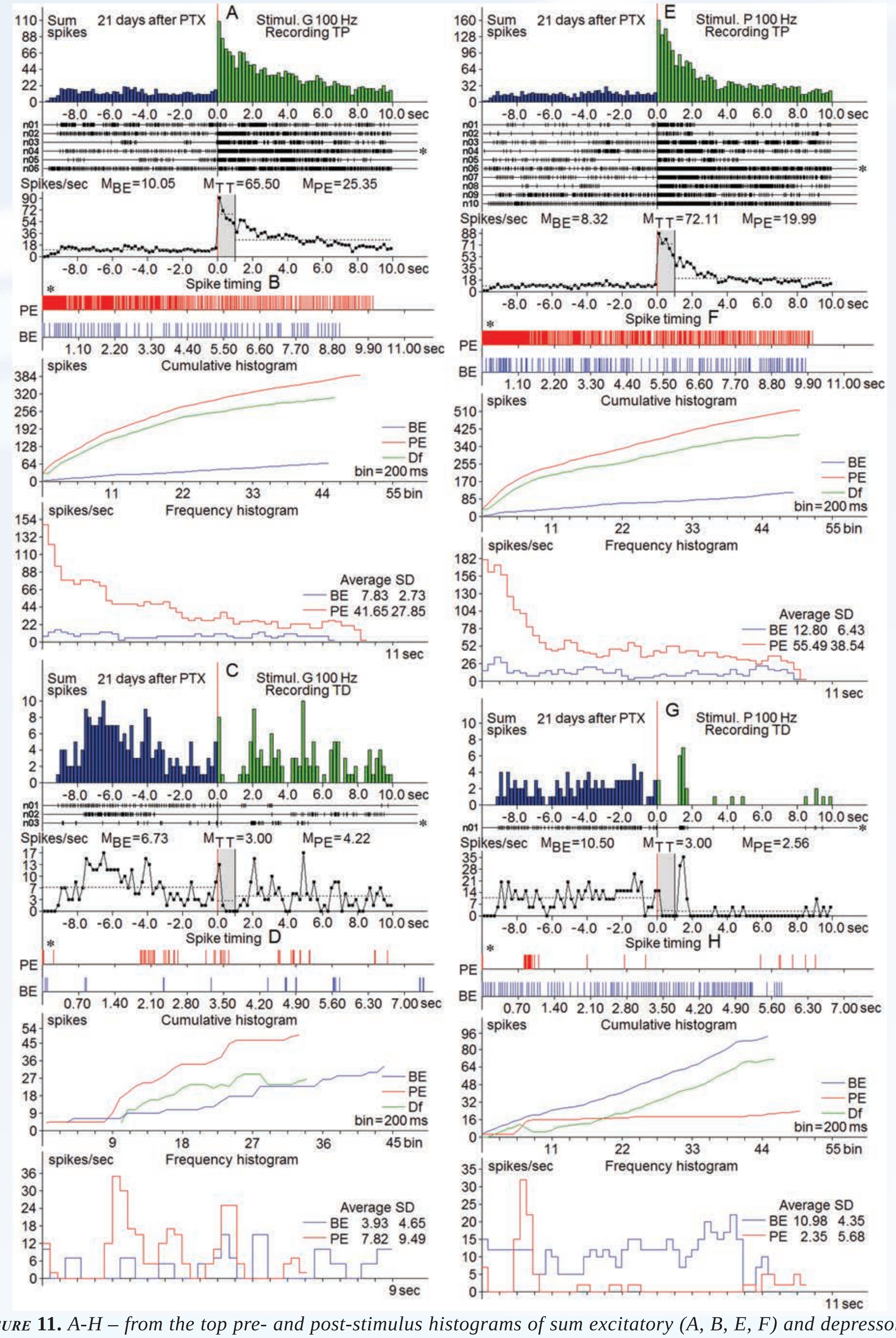

***FIGURE* 11.** *A-H – from the top pre- and post-stimulus histograms of sum excitatory (A, B, E, F) and depressor (C, D, G, H) displays of spike activity in real time (20 sec before and after stimulation) of single spinal cord motoneurons at the 21st day after PTX, evoked by 100 Hz HFS of nerves G (A-D) and P (E-H).*

There is no correlation between the length and localization of calcification foci and neurologic abnormalities;

Hypoparathyroid patients with focal calcification in the central nervous system require long-term multi-disciplinary medical and neurophysiological imaging and neuropsychological monitoring [*Roztoczyńska D. et al., 2010*].

Pathological calcification, being the most common case of hypoparathyroidism and pseudohypoparathyroidism undertakes to diverse occasions such as metabolic diseases, infections and genetic diseases. Physiological intracranial calcification occurs in 0.3-1.5% of cases; it is asymptomatic and determined by chance when neuroimaging. In addition, tetany and seizures are presented as Parkinsonism and dementia. Since adequate treatment of hypoparathyroidism can lead to significant clinical improvement, then for all individuals with the basal ganglia calcification (BGC) it is proposed to determine the plasma concentration of Ca^{2+}, phosphorus and PTH levels, in order to avoid hypoparathyroidism [*Basak R., 2009*]. Data on the prevalence and progression of BGC and its pathogenetic mechanism are presented in patients with idiopathic (of unknown origin) hypoparathyroidism (IHP) and the factors determining its progression. The occurrence of hypoparathyroidism in hypocalcemic medium is due to development of high plasma calcium-phosphorus. Researchers concluded that BGC is found in 73.8% of patients with IHP and correlates with the duration of hypocalcemia of choroid plexus calcification, convulsions, and cataracts, which extends the importance of adequate phosphorus control in hypoparathyroidism management [*Goswami R. et al., 2012*]. In turn, congenital hypoparathyroidism covers diseases characterized by common biochemical features of symptomatic hypocalcemia with concomitant hyperphosphoremia, but differing in the clinical features dictated by a specific genetic disease. Various diseases attributable to both hypoparathyroid and pseudohypoparathyroid conditions, with detailed message of the recent discoveries in terms of genetics common to these syndromes [*Brandi M., 2011*] are surveyed. Finally, hypocalcemia induced epilepsy is often diagnosed as idiopathic epilepsy. Therefore, a mandatory part of diagnostic algorithm should be a standard assessment of Ca^{2+} levels in plasma of patients with newly-identified epileptic seizures. In other words, epileptic seizures serve as the first signal of hypoparathyroidism [*Pesić M. et al., 2011*].

Recent data on the IHP myopathy and histological method of its pathogenesis are of interest. In general, patients with IHP have some non-specific histological changes in skeletal muscle, an inverse relationship between reduced levels of plasma Ca^{2+} and elevated plasma levels of muscle enzymes, which have been attributed to hypocalcemia. In addition, the severity of changes in muscles relates not only to its degree, but duration of hypocalcemia [*Dai C. et al., 2012*]. Further, it was found that chronic hypocalcemia could cause EEG changes and mimic myocardial infarction, as well as reversible cardiac dysfunction. On the other hand, cardiomyopathy and heart failure are revealed in patients with IHP. In other words, the 2 diseases of Ca^{2+} homeostasis can cause severe hypocalcemia with clinical manifestations of the last stage of heart failure. In addition, severe heart failure irreversibly occurs after Ca^{2+} saturation, suggesting a permanent dysfunction of the heart muscle, obliged to combined cardiomyopathy [*Mavroudis K. et al., 2010*]. The hypocalcemia might be a complication of PTX. As found, the reduction of intraoperative PTH levels above 85% after PTX might be considered a reliable predictor of postoperative hypocalcemia after PTX in primary hyperparathyroidism [*Crea N. et al., 2012*]. The functional hypoparathyroidism in postmenopause women with brittle bones [*Amouzougan A. et al., 2012*] is also of interest. Finally, pregnancy and lactation are associated with significant changes in Ca^{2+} homeostasis, as a result of alterations in the development, metabolism, and excretion of Ca^{2+} and Ca^{2+}-tropic hormones. Therefore, both the clinical course of disease affecting parathyroid glands during pregnancy and lactation, and their diagnosis are often atypical and difficult. Hypoparathyroidism is a disease state rarely observed during pregnancy and in most cases it is resulting from the surgical thyroidectomy [*Krysiak R. et al., 2011*].

The present study provides the excitatory and depressor post-stimulus tetanic and posttetanic activity of SC MNs to stimulation of the extensor and flexor collateral branches of the sciatic nerve in the dynamics of hypocalcemia development at 3-7 and 21-22 days after PTX. In this study it was of interest to estimate the ratio of expression and dynamics of the rising time of depressor and excitatory responses. We should briefly dwell on recent studies in this direction. The powerful mechanism of synaptic plasticity is displayed as switching long tetanic potentiation (LTP) into depression (LTD) – "switch LTP to LTD" – via regulation of Ca^{2+} endoplasmic reticulum local stocks, as shown by the example of inositol triphosphate-induced modulation of synaptic plasticity by transient increase in Ca^{2+} through voltage-dependent channels [*Stutzmann G. et al., 2004*]. Previously the PTP of inhibitory post-synaptic potential (IPSP) through the accumulation of Ca^{2+} in the presynaptic terminals was described. In this case, the use of Baclofen, an inhibitor of presynaptic calcium propagation through N and P/Q-type Ca^{2+} electrogenic channels (ECC) led to threefold increase of PTP, unlike the non-specific reduction of Ca^{2+} occurrence [*Jensen K. et al., 1999*]. The same authors showed the new presynaptic regulatory mechanism in fast CNS synapses, associated with the involvement of L-type channels. Moreover, L-type ECC did not participate in the low-frequency synchronous release of transmitter, but contributed to the accumulation of presynaptic Ca^{2+} during high-frequency activation, which helped to support the release of vesicles during tetanic stimulation and to increase the expectancy of mediators release during posttetanic period with the formation of PTP [*Jensen K. et al., 1999*]. With small changes in concentrations of extracellular Ca^{2+} and Mg^{2+} the high excitability and burst discharge were described to alter gain of LTP, epileptogenesis and neuronal damage [*Wang T. et al., 2004*]. In general, the results obtained in the present study, as compared to norm, were as follows. Background activity in the flexor MNs to HFS of flexor nerve decreased at the 3rd day and was growing progressively from days 4-5 (up to 1.5 times), fit to 1.1-fold underestimation at the 22nd day, while that of extensors, growing to the 4th day, reduced up to the same value at day 22. At 50 *Hz* HFS of G nerve, only on the 22nd day MNs TP approached the norm, while at 100 *Hz* in all the days of testing TP was higher the norm, progressively growing 4.7-fold. At 50 *Hz* HFS of nerve P, starting from day 7 the TP of MNs increased to 1.6-fold excess of norm, while in response to 100 *Hz* it was greater than norm already since day 3, still growing progressively to the 22nd day, as in the case of nerve G. The MNs TD under 50 *Hz* HFS of nerve G, increasing from the 4th to the 21st day reached 2.3-fold excess of norm, and at 100 *Hz*, – from day 4 to 7 twice exceeding the norm; then by day 21 TD dropped to 1.5 times. The MHs TD at 50 *Hz* HFS of nerve P, already since day 4 and on day 21 reaching a 1.5-fold excess, approached the norm by the 22nd day. At 100 *Hz*, this value, though being 3 times higher than norm by day 4, decreased up to twofold excess of norm at day 7, reaching the norm by to the 22nd day. Thereby, with development of pathology there was recorded a sharp increase in tetanic excitatory effects. As for tetanic depressor effects, along with their sharp increase during tests by termination they were exhausted, reaching the norm. Thus, their protective features ceased to operate, as will be discussed below. The PTP and PTD in MNs to HFS of the both nerves, likewise the norm, accompanied TP in all terms. The TD of MNs to HFS of G nerve changed into the PTP in the early days and into PTD – in late terms, whereas TD of nerve P changed equally in both terms, though in norm TD from both nerves changed into PTP at 100 *Hz* and into PTD at 50 *Hz*.

In recent decades, due to the increase of neurodegenerative diseases the utmost importance is attached to disorders of neurotransmitters interaction in the synchronization of neural networks. In a number of neurodegenerative diseases the disorders of communication links in various neurotransmitter systems are shown, in particular, those between glutamate and GABA-ergic systems. Deepening of the depressor tetanic reactions is apparently the result of their nomination as bearing protective load at the early stages of recovery. The assumption on universal protective function of GABA-ergic inhibition was also supported by the evidence of published data showing that in some systems – during the nervous system development – GABA acted as an agent on the various features, including proliferation, migration, as well as differentiation and maturation of synapses, cell death and expression of GABA(A) receptor [*Cuppini R. et al., 2002*]. Furthermore, it was supposed that GABA and glycine might play an important role and possess the ability to change not only in developing, but also in mature central vestibular system [*Owens D., Kriegstein A., 2002*]. In turn, the crucial role of events mediated by GABA receptor in neurons of the vestibular nuclei in the recovery of function after unilateral labyrinthectomy, known as vestibular compensation, was established [*Johnston A. et al., 2001; Tighilet B., Lacour M., 2001; Giardino L. et al., 2002*]. Moreover, modern studies on the cellular and network levels demonstrate that the synaptic inhibition cannot be assessed only as opposed to synaptic excitation and additionally serves highly specific functions in the nervous system of mammals [*Birke G., Draguhn A., 2010*]. According to our data, depressor response is more intensively involved both in the non-specific (peripheral and central) and specific neurodegeneration in different parts of the brain [*Sarkissian J. et al., 2007; Galoyan A. et al., 2008; 2010*].

According to data of this study, with the increase of excitatory post-stimulus activity displays in MNs of SC there was also a similar gain of depressors that reached the norm only by the end of testing, but did not contribute to the achievement of those excitatory norms highlighting the need for the appropriate pharmacological intervention, in order to strengthen the protective activity of depressor responses and restore normal balance of post-stimulus excitatory and depressor responses.

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