Self-Initiated Behavioral Act-Related Neuronal Activity in the Region of the *Raphe* Nuclei of the Cat

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Neirofiziologiya/Neurophysiology, Vol. 36, No. 1, pp. 56-64, January-February, 2004.

Received April 21, 2003.

In experiments on awake cats, we recorded the activity of 79 putative serotonergic (STE) neurons localized within the region of the brainstem dorsal and anterior central *raphe* nuclei. The animals were trained to perform a self-initiated (voluntary) movement, to press a pedal by the forelimb; an additional limitation was to perform the movement not earlier than after a definite time interval. Changes in the activity of STE neurons related to the preparation for and performance of the movement and reactions to presentation of a feedback conditioning signal preceding the reward and receipt of the food reward were most clearly manifested. More than 50% of the units changed their activity before the movement initiation. Most neurons responded to presentation of a positive conditioning signal by phasic activation, while a negative signal informing them of the absence of the reward evoked considerably weaker reactions. We hypothesize that reactions of STE neurons forestalling the movement initiation can provide activation of the neocortex necessary for the movement performance within a preset time interval. Activating and inhibitory reactions observed within the period of expectation of a feedback conditioning signal and developing after presentation of this signal can be related to a noticeable role of the STE system in the formation of memory engrams and development of emotional states.

Keywords: *raphe* nuclei, serotonergic neurons, conditioning, time counting off, voluntary movement.

INTRODUCTION

Monoaminergic systems of the brainstem, which project to different CNS structures (including the neocortex), play a highly important role in organization of the targeted behavior. In general, monoaminergic neurons themselves are not members of the most important sensory and motor cerebral systems, but efferent fibers of these cells innervate both primary and secondary sensory structures and motor centers and exert significant regulatory influences on these structures [1]. The serotonergic (STE) system is one of the monoaminergic systems; most its neurons are localized within the brainstem *raphe* nuclei (RN). The STE system is believed to be the most ramified system among the monoaminergic systems in the vertebrate brain [2]. Neurons of the STE system send numerous ascending and descending efferent fibers to different brainstem nuclei and to other cerebral regions, and these fibers form a huge number of terminals in their projection zones. STE innervation of the neocortex is provided by an anterior (mesencephalic) group of the RN; these are, first of all, the dorsal and anterior central RN. The density of STE fibers in the neocortex is in general greater than that of noradrenergic (NAE) fibers [1, 3]. STE innervation is the densest in those cortical sites where fibers of the NAE system are less numerous (e.g., in the layers of stellate neurons, but not in the "pyramidal" layers). This allows one to speculate that the above systems are supplementary to each other. In any case, the density and spatial distribution of STE fibers are sufficient to provide innervation of all neocortical neurons by STE inputs. In the cat, most neurons of the RN were shown to project their axons to the forebrain structures via the contralateral medial longitudinal fasciculus, whereas some cells possess bifurcated axons and innervate forebrain structures of both hemispheres [1, 4, 5].

Similarly to neurons of other aminergic systems,

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0090-2977/04/3601-0050

STE cells influence target units not only by releasing their neurotransmitter via "classic" synaptic connections, but also via varicose expansions of the axon terminals [5, 6]. In the latter case, serotonin (ST) is released into the intercellular space; this allows the neurotransmitter released by a single fiber to influence a number of the target neurons. The effects of ST are mediated by post-synaptic receptors localized on the dendrites of target neurons and their spines, by pre-synaptic receptors on the axon terminals contacting the above target cells, and by autoreceptors. At present, at least seven different types of ST receptors and 15 of their subtypes have been identified within the CNS; this allows ST to exert specific (to a greater or a lesser extent) effects in one situation or another. Serotonin is not only capable of changing the membrane potential of the target neuron (in such a manner directly inhibiting or facilitating the activity of the latter); it also can modulate the effects of other transmitters on this cell [6, 8].

Earlier, ST was thought to exert mostly inhibitory effects on the activity of target neurons. At present, it is believed that ST, in contrast to noradrenaline (NA), actually suppresses synaptically evoked neuronal responses in many brain regions; these effects can be interpreted as a decrease in the signal/noise ratio in the course of information processing. At the same time, ST mostly enhances neuronal reactions in brain structures involved in motor functions [6, 9]. Some researchers even hypothesize that the STE system, together with the acetylcholinergic (AChE) system, forms a common final pathway for a few parallel ascending systems responsible for general activation of the cortex [10-12].

Serotonergic neurons possess properties similar to those of other monoaminergic neurons. They generate the background activity (BA); it cannot be ruled out that this activity is not evoked by a background synaptic inflow but is actually spontaneous (some authors qualify this activity as pacemaker-like). In the normal awake state of the animal, the mean frequency of this activity usually varies in different cells from 0.5 to 6 sec^{-1}, and action potentials are rather long-lasting (their duration is about 2-3 msec). Usually, the frequency of spiking of STE neurons increases with intensification of the behavioral activity, positively correlates with general intensity of the motor activity, and increases to 10-12 sec^{-1} during eating and grooming accompanied by rhythmic movements. The activity of STE cells increases with an increase in the tone of body muscles, during locomotion, and with stroking of the head and neck of the animal. Presentation of simple acoustic and visual stimuli evokes short-term impulse responses of STE neurons (latencies within 40 and 64 msec ranges, respectively); these responses are followed by about 200-msec-long suppression of the BA. During orientation reactions and research behavior, the BA of STE neurons is suppressed [5, 6, 9].

Analyzing the role of the STE system in central motor control mechanisms, the authors of a few detailed reviews have concluded that the most important functions of this system are the following: it facilitates tonic and cyclically organized motor outputs, prepares the organism for realization of the movements, and integrates relatively simple movements in complex behavioral acts [2, 5, 6]. Under these conditions, the STE system inhibits sensory processing and coordinates autonomic and neuroendocrine functions with the motor behavior. In a relaxed awake state, impulsation of STE neurons is relatively low-frequency and rhythmic; this, probably, reflects generation of the endogenous pacemaker activity. As a result, the level of synaptic ST release is relatively low and stable; it provides a tonic "excitatory drive," which exerts a modulatory influence on the neuronal activity in the motor system. Suppression of the sensory information processing, which could interfere with the organization of discrete movements, is provided by inhibition of target cells in the cortex and subcortical structures due to an ST-induced decrease in the signal/noise ratio in afferent neuronal networks responsible for the above processing. Under certain conditions (appearance of new nonstandard stimuli), the situation is reversed; the STE system is inactivated, the motor output becomes relatively defacilitated, while sensory processing undergoes disinhibition [2, 13].

Such a role of STE neurons in the control of behavioral states and sensory processing allows one to conclude that the function of the STE system is related to the control of higher mental functions and realization of various complex behavioral acts. This system is believed to be involved in the formation of reactions conditioned by the emotional influences and process of learning [5]. It is thought that the STE system in the normal state is actively involved in the formation of memory traces, by exerting correcting influences on the efficiency of cortico-cortical synapses (supposedly, ACh- and GABA-ergic) [14, 15]. The type of such influences is determined by the emotional "color" of the corroboratory stimulus. Destruction of the RN impedes learning with the use of a food reward but facilitates the formation

of a conditioned active avoidance reaction; this gave rise to the concept of the leading role of ST in the formation of an emotionally positive state. The involvement of the STE system in consolidation of the memory traces is supposed to be related to the capability of ST to prolong repetitive circulation of excitation in neuronal systems responsible for the emotionally positive perception and memorization of the latter. In this case, the integral effect of ST is reciprocal to the effect of NA [16].

All the above considerations allow one to conclude that the STE system of the RN is a crucially important association, which significantly regulates cerebral functions and triggers and commutates different behavioral states. At the same time, functional specifities of the above system, including the pattern of neuronal activities in the dorsal and central RN, have been insufficiently studied. On the one hand, it is known that neurons of these nuclei are not intensively involved in organization of noncyclic (sporadic) targeted movements, of motor responses triggered by an acoustic or a visual signal [9], and of such a cyclic motor phenomenon as locomotion [17]. On the other hand, electrical stimulation of the dorsal and central RN, as well as the influence of ST agonists, evokes activation of the neocortex in awake rats; this is accompanied by motor hyperactivity (intensification of locomotion and voluntary targeted movements). These observations allowed experimenters to conclude that activation of the cortex (with a motor or another behavioral act as the final result) is the main function of the STE system [10-12].

Thus, the question on the involvement of the dorsal and central RN in the triggering of self-initiated movements (e.g., movements performed not after a signal, but with a certain delay with respect to the preceding one) remains open. It is still unknown how neurons of the RN respond to presentation of conditioning stimuli, which possess a positive or a negative "color" and forecast whether the response will be rewarded or not. Earlier, we showed that neurons of other adrenergic systems, the dopaminergic (DAE) or NAE system, are rather actively involved in the organization of self-initiated movements and perception of conditioning stimuli [18, 19]. This is why we tried in this study to describe the pattern of reactions of STE neurons localized within the region of the dorsal and central RN; these reactions were related to the performance of integral behavioral acts, including self-initiated movements and perception of conditioning signals informing on the presence or absence of the reward after such a movement.

METHODS

Experiments were carried out on two awake cats trained to perform the operant behavior (when trying to obtain food reward, to lift the right forelimb from a platform and to press a pedal) [18, 19]. Only those trials were rewarded where the animal held the limb on the platform for not less than 4 sec and pressed the pedal not earlier than 12 sec after the preceding movement. When the task was performed correctly, a long-lasting conditioning sound signal was presented, 1 sec after pressing the pedal; then after a 1.0- to 1.5-sec-long interval the animal obtained a food reward. When the trial was incorrect, it was followed by a negative conditioning signal.

After training, the animals were operated under general anesthesia (nembutal, 40 mg/kg, i.p.). A conductor plug was implanted; its tip was localized 10 mm above the dorsal RN. The plug was inserted obliquely, at a 20° angle with respect to the frontal plane and at a 15° angle with respect to the sagittal plane. Later on, the neuronal activity was recorded contralaterally to the working limb, within a zone with the following coordinates: P –1…–2, L 2…0, and H 5…9 mm (Fig. 1). This zone corresponds to

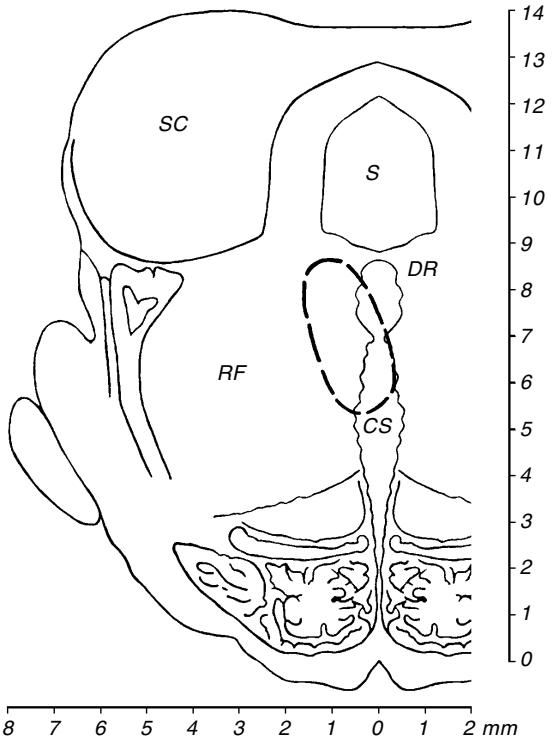

Fig. 1. Scheme of localization of the zone of recording (shown by a dashed line) from putative serotonergic neurons in the cat brainstem. The section of the brain corresponds to the P –2.0 frontal plane (according to the Reinoso-Suarez atlas [20]). SC are the superior colliculi, S is the Sylvian aqueduct, RF is the reticular formation, and DR and CS are the dorsal and superior central *raphe* nuclei.

the dorsal and superior central RN, where neurons projecting to the neocortex are localized [20, 21]. To verify the recording region, the respective sites were labelled with electrocoagulation. The animals were euthanized by injection of a nembutal overdose; the brain was fixed in formalin, and slices were prepared using a freezing microtome. Other details of the technique were described earlier [18, 19].

RESULTS AND DISCUSSION

In our experiments, the mean interval between the realizations of self-initiated behavioral acts performed by the animals was 18.5 ± 0.6 sec (here and below we show means ± s.e.m.); the extremum values were 5.5 and 120.4 sec. The earliest changes in the EMG recorded from the right forelimb flexors and corresponding to initiation of the movement were noticed 240 msec before lifting the forelimb from the platform [18]. The mean duration of the movement (from lifting the forelimb until pressing the pedal) was 418.2 ± 4.3 msec (extremum values 214 and 979 msec). In our tests, the proportion of the correctly performed and, correspondingly, rewarded trials was 50-80%.

In general, the activity of 79 neurons was recorded within the examined region (dorsal and central RN). These cells generated a single-spike or, less frequently, a grouped BA, whose mean intragroup frequency was 2.1 ± 0.2 sec^{-1} (lowest and highest values, 0.1 and 6.0 sec^{-1}). Action potentials were polyphasic and long-lasting (2.5 to 3.0 msec). Such characteristics allow us to postulate that the above nerve cells localized in the RN region are the putative STE neurons.

The examined cells changed their activity throughout the performed behavioral act. Changes related to preparation for, triggering of, and performing of the voluntary movement, as well as responses to presentation of the conditioning acoustic signals informing about the reward and to receiving the reward *per se*, were expressed most clearly (Figs. 2 and 3). Changes in the discharge frequency,

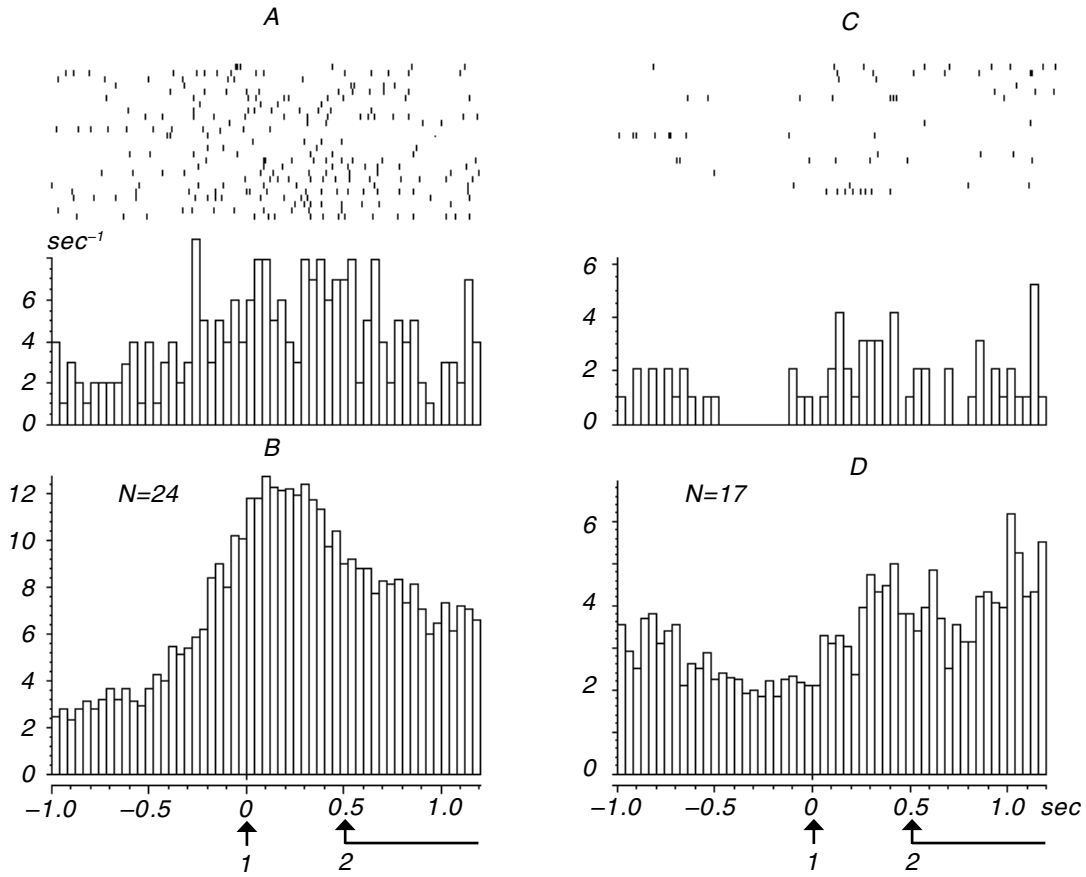

Fig. 2. Reactions of the putative serotonergic neurons of the dorsal and superior central *raphe* nuclei that were activated (A, B) and inhibited (C, D) before the beginning of self-initiated movements. A and C) Activity of two single neurons (above and below, raster diagrams and corresponding histograms, respectively); B, D) averaged normalized histograms. Histograms are plotted with respect to the moment of EMG initiation shown by arrow 1; arrow 2 shows the moment of pressing the pedal. Abscissa) Time, sec; ordinate) frequency of action potentials, sec^{-1}; *N* is number of the neurons; bin width, 40 msec.

TABLE 1. Types of Changes in the Activity of 79 Putative Serotonergic Neurons of the Region of the *Raphe* Nuclei Related to Different States of the Behavioral Act

Stage of the behavioral act	Changes in the activity		
	activation	inhibition	no changes
Preparation for the movement	24 (30.4)	17 (21.5)	38 (48.1)
Performance of the movement	33 (41.7)	18 (35.4)	28 (35.4)
Pressing the pedal	22 (27.9)	23 (29.1)	34 (43.0)
Expectation of the conditioning signal	22 (27.9)	24 (30.4)	33 (47.8)
Presentation of the positive signal	46 (58.2)	7 (8.9)	26 (32.9)
Receiving of the reward	67 (84.8)	0	12 (15.2)
Presentation of the negative signal	22 (27.8)	14 (17.7)	43 (54.4)
Absence of the reward	18 (22.8)	7 (8.9)	54 (68.4)

Footnote. Normalized numbers of neurons, %, are shown in parentheses; total number of the neurons is taken as 100%.

TABLE 2. Power of the Excitatory and Inhibitory Reactions of Putative Serotonergic Neurons of the Region of the *Raphe* Nuclei Related to Different Stages of the Behavioral Act

Stage of the behavioral act	Normalized changes in the activity, %	
	activation	inhibition
Preparation for the movement	170.1 ± 35.8 (15.5 – 695.0)	–52.0 ± 7.7 (–12.2 to –100.0)
Performance of the movement (in general)	252.8 ± 61.9 (23.8 – 1209.2)	–47.8 ± 7.3 (–19.5 to –100.0)
Triggering of the movement	217.3 ± 46.3 (27.6 – 1136.9)	–36.9 ± 7.1 (–22.3 to –100.0)
Development of the movement	316.7 ± 73.4 (16.9 – 1339.3)	–67.1 ± 7.8 (–13.1 to –100.0)
Pressing the pedal	277.8 ± 64.4 (39.0 – 1145.0)	–43.7 ± 6.4 (–12.8 to –100.0)
Expectation of the conditioning signal	210.2 ± 62.1 (19.2 – 1168.5)	–42.0 ± 5.6 (–42.0 to –100.0)
Presentation of the positive signal	224.2 ± 48.7 (13.5 – 1488.2)	–35.5 ± 3.4 (–29.4 to –41.2)
Receiving of the reward	390.7 ± 101.8 (31.1 – 3948.0)	–
Presentation of the negative signal	80.7 ± 17.4 (17.7 – 213.7)	–64.9 ± 11.9 (–12.0 to 100.0)
Absence of the reward	116.1 ± 49.2 (19.9 – 492.0)	–70.1 ± 13.3 (–18.9 to 100.0)

Footnote. Means and s.e.m. are shown; extremum values are shown in parentheses.

which exceeded a doubled s.d. from the mean value of the above parameter, were considered significant. When correlated with the key moments of the behavioral act, neuronal reactions were characterized by the following indices. Neurons whose responses were related to preparing for and triggering of the movement were activated, on average, 304.3 ± ± 44.4 msec before an increase in the EMG amplitude (the earliest reactions forestalled the movement by about 980 msec). Inhibition of the neuronal activity, which preceded the movement, developed, on average, 401.1 ± 65.7 msec before initiation of the EMG response (the earliest reactions of this type began about 760 msec before the movement). Responses to presentation of the conditioning positive and negative reward-related signals were, in most cases, of an excitatory nature and developed with the mean latencies 53.0 ± 3.4 msec (extremum values 32-120 msec) and 59.1 ± 7.8 msec (32-130 msec) with respect to the moments of presentation of these signals.

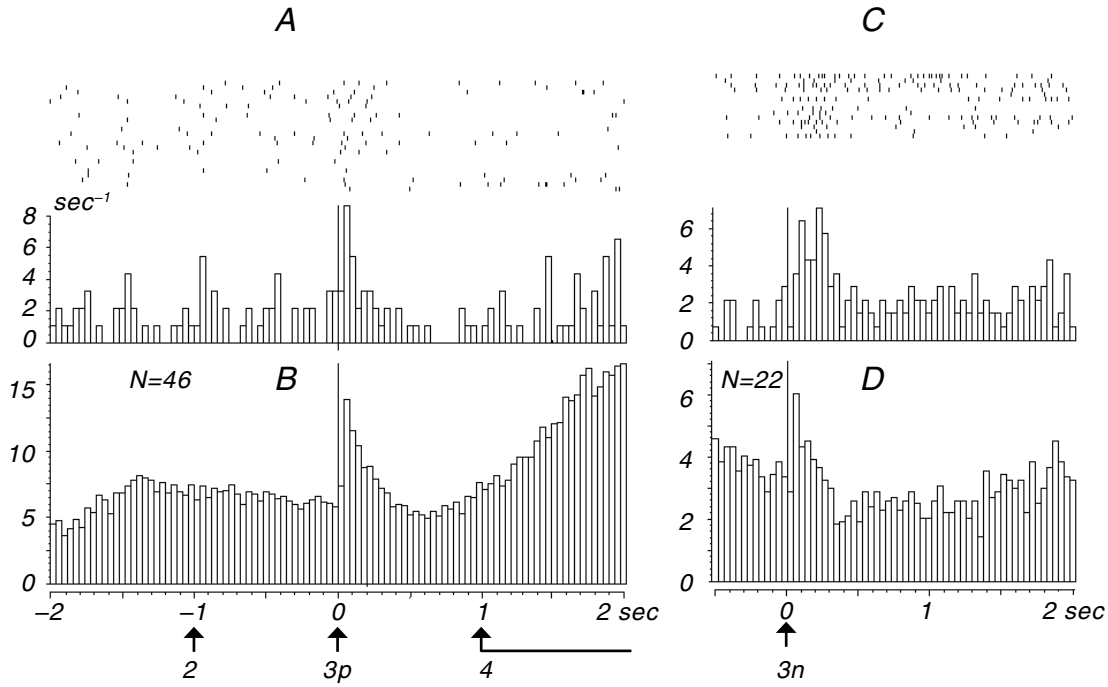

Fig. 3. Reactions of the putative serotonergic neurons of the dorsal and superior central *raphe* nuclei related to pressing the pedal and presentation of positive (A, B; shown by arrow 3p) and negative (C, D, shown by arrow 3n) conditioning signals, and to receiving of the reward (shown by arrow 4). Histograms are plotted with respect to presentation of conditioning signals. Other designations are similar to those in Fig. 2.

Similarly to what was made in our earlier studies [18, 19], the behavioral phenomenon under study was divided into a few periods (time windows) that made possible separate estimation of the direction and power of the responses within these windows. These were preparation for the movement (–300…0 msec with respect to the EMG burst), performance of the movement (0…390 msec after the above moment), pressing the pedal (0…255 msec after switching on of the pedal sensor), expectation of the conditioning feedback signal (–745…0 msec before presentation of the latter), a response to presentation of this signal (20…160 msec), and a response for receiving the reward or the absence of the latter (1-2 sec after the signal). Data on the number of neurons that were activated or inhibited within the above time intervals and on the power of these reactions are shown in Tables 1 and 2, respectively. In Table 2, the period of performance of the movement has been additionally subdivided into two stages, triggering of the movement (from EMG initiation to switching on of the sensor, which indicated lifting the limb from the platform, 0…240 msec with respect to the moment of EMG burst) and the development of the movement (0…150 msec after switching on of the platform sensor).

First, the following finding deserves attention. The majority of the putative STE neurons of the RN region changed their activity within the periods of preparing for and realization of the movement (Table 1). The number of activated neurons in this case was somewhat greater than that of inhibited units. Other authors who examined the reactions of the RN neurons reported that the activity of STE neurons either remained unchanged or was inhibited during targeted movements [2, 9]. Under our experimental conditions, the movement was self-initiated, and it was performed within a relatively limited time interval. This situation forced the animal to fix its attention on providing voluntary triggering of the movement just within this interval, i.e., it probably provided initiation of the activity specifically related to a motor component of the task. As was mentioned above, triggering of the process of activation of the neocortex, which is clearly manifested electrographically, can be one of the most important functions of the STE system [11].

When we analyzed the power of movement-related reactions of STE neurons, we found the following. The power of excitatory reactions reached its maximum within the stage of development of the movement; the mean intragroup impulsation frequency increased by about four times as compared with the initial value

(Fig. 2, Table 2). The power of reactions remained rather high within all periods and stages of the movement, until the moment of pressing the pedal. We can hypothesize that such a pattern of the reactions of STE neurons is related to the following requirement: It is necessary to maintain a certain level of activity of the CNS motor centers within the entire period of the movement.

Within the period of expectation of a conditioning signal, most cells generated responses (changes in their activity), and nearly equal proportions of the neurons were activated and inhibited. The frequency of spiking of the activated cells was, on average, three times higher than the background frequency. As is known, a contingent negative variation (CNV) can be recorded from the cerebral cortex within this period; generation of this potential is related to expectation of a relevant sensory signal, concentration of attention, preparation for a movement, and to the movement in general [22]. The correlation between the activity of the STE system and CNV pattern has been examined in single studies, and the results of the respective analysis are contradictory. In early studies, the peculiarities of the CNV in patients with endogenous depression were described. It was shown that L-tryptophan and other agents promoting an increase in the ST level suppress the CNV [23-25]. Later studies on healthy persons, however, showed that in the norm the CNV amplitude in the frontal neocortical regions correlates positively with the activity of the STE system [26]. The complex nature of the STE influences can probably be related to a well-known feature, the non-monotonic (V-shape) dependence between the levels of neurotransmitters and CNV amplitude (the amplitudes of other slow endogenous EEG potentials demonstrate similar nonlinearities) [23]. Our data on opposite directions of movement-related reactions in the neuronal population of the dorsal and central RN observed within the period of waiting for a signal also show that neuronal units in this region can be involved in generation of the CNV in various manners. Stable activation of a part of the putative STE neurons during expectation of a feedback signal can be one of the sources of extrathalamic subcortical influences responsible for CNV generation.

Most RN neurons under study were phasically activated after presentation of the positive conditioning signal, while about one quarter of the cells demonstrated excitatory reactions to presentation of the negative signal (Fig. 3, Table 1). Such phasic reactions under conditions of the experimental paradigm used were observed earlier in DAE and NAE neurons of the cat [18, 19]. As was mentioned earlier, in our experiments these signals possessed dissimilar emotional coloring; they forecasted either the presence or absence of the food reward in the future. In this relation, it should be emphasized that the power of responses of STE neurons to presentation of the positive stimulus was two or three times greater than that related to the negative signal. This phenomenon can depend on the higher level of involvement of RN neurons in the genesis of positive emotions. In our experimental situation, phasic activation of the RN neurons evoked by positive signals informing on the successful performance of the task can also be related to generation of the P300 EEG potential recorded in this experimental paradigm [27]. Reports on the presence or absence of any contribution of the STE system to generation of the P300 or to modulation of the amplitude and latency of this wave are contradictory [28]. Our results prove the former statement (STE neurons can be involved in the development of P300).

After presentation of the food reward, most STE neurons under study were activated, and these reactions were characterized by the greatest intensity, as compared with those observed during other phases of the behavioral act. When there was no reward, mostly inhibitory reactions of STE neurons were observed (Table 1, Fig. 3).

Therefore, our study demonstrated that STE neurons of the anterior RN group, similarly to neurons of other monoaminergic systems, considerably change their impulsation within different stages of the targeted behavioral act. In this context, STE neurons should not be considered the cells immediately involved in initiation of the movement and control of the motor event. This neuronal system, similarly to other aminergic systems, is most likely responsible for the formation of a certain background necessary for realization of the integral behavioral act (under our conditions, a self-initiated act). Reactions of STE neurons, which considerably forestall the beginning of the movement, can provide activation of the neocortex necessary for the performance of the movement within the preset time interval [10, 11]. The activating and inhibitory reactions observed within the period of expectation of feedback conditioning signals and after their presentation are probably related to the role of the STE system in the formation of the memory trace and the development of the emotional states. These responses can to a certain extent provide plastic modifications of synaptic connections in the neocortex, which develop in the course of the conditioned reflex activity.

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