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Influence of Chronic Psychogenic Stress Repeated in Genetically Linked Generations of Rats on Typological Peculiarities of Offspring Behavior. Emotionality, Locomotion, Stress-Reactivity

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ABSTRACT. In 370 adult offspring of five consecutive generations of initial 8 pairs of offspring rat-parents crossbred in the state of a strong psychogenic stress (information neurosis) in the open field the indices of emotionality (defecation and motor activity level) have been studied in their initial status, i.e. before any experimental procedures as well as after a moderate stress (elaboration of two-way active avoidance). It has been established that a pronounced information pathology of rat-parents induces considerable changes in offspring behavior expressed in: an enhanced emotionality with pronounced anxiety, followed by an increased locomotion and excretory function, an increased excitability and its low threshold, high stress-reactivity and large stress response unequal to an action exposure. The above-said changes progressively increase from second to consecutive generations of continuous lines of the offspring. The first generation of direct offspring of stressed rat-parents does not show any significant changes in behavior.

The results obtained are discussed from the standpoint of existent views about the character of interrelations of emotionality signs in the open field as well as in the aspect of possible ways of formation of stress-induced affective disorders and ways of their effect on the hereditary apparatus. *© 2008 Bull. Georg. Natl. Acad. Sci.*

Key words: *psychogenic stress, offspring, open field, emotionality, locomotion, stress-reactivity.*

Introduction. One of the basic principles of the genetics of higher nervous activity is the position that the peculiarities of conditioned reflex activity and main features of the process of the nervous system (excitability threshold, conduction velocity of neural impulse, intensity of the excitatory process and its generalization) are genetically determined, while the variations of these signs show phenotypic (within the limits of the norm of the given genotype) and genotypic (related to the heterogeneity of allele content of the genotype) variability as well as any other signs of the organism [1, 2].

However, for the signs of behavior the genetics of higher nervous activity singles out one more - special form of variability connected with the impact of individual experience, i.e. with different forms of learning, sensitization, habituation, formation of imagery, etc. This form of variability reflects the specificity of the brain as a structural basis for adaptive behavior [1-3]. M.E. Lobashev named the transfer and fixation in generations of an individual experience of adaptation to environmental factors, based on conditioned reflex activity from definite stages of the ontogenesis of higher animals, signal hereditary [3].

An obvious illustration of the permanent changes in congenital behavior under the influence of repeated environmental factors acting through many generations is the history of the taming of wild beasts by man and special selective programs of domestication of fur-bearing animals. The changes occurring in the behavior are conditioned by stress induced by new conditions of life and are accompanied by complex transformations endocrine and neurotransmitter systems [4].

The influence of maternal stress ("maternal effect") on the offspring's behavior has been studied for a long time, becoming the subject of study of an increasing the number of works [5-8, etc.]. The available data point to the feasibility of change of emotionality, motor activity [5-8], learning [6] of the offspring of stressed mothers.

The biological universality of stress phenomena and its possible influence on the hereditary apparatus make for the exceptional importance of genetic investigations in this direction.

Proceeding from the above-said, we set ourselves the task of studying the influence of experimental information neurosis repeated in continuous line of genetically connected generations of rats on typological peculiarities of the behavior and the learning of their offspring.

In the present paper a part of the results of this investigation is presented regarding the characteristics of the emotionality, motor-exploratory activity and stress-reactivity of the offspring of five generations of closely-related cross-breeding of direct offspring of eight initial pairs of rat-parents with pronounced information neurosis. Information neurosis was worked out according to the original methods of avoidance of psychogenic stress, proposed by M.M. Khananashvili and T.R. Domianidze [9].

Materials and Methods. The investigation was carried out with 386 white outbred rats of both sexes, weighing 150-300 g.

From the first direct offspring (F1) of initial, eight pairs of parents in the state of strong chronic psychogenic stress by means of sibling cross-breeding of four consecutive generations were again obtained (F2-F5) with an overall number of 370 F1-F5 offspring.

Modeling of information neurosis. The method of psychogenic stress, proposed by Khananashvili and Domianidze, is based on the integration of two conditioned reflexes of bilateral active avoidance (CRAA).

The experimental apparatus is a modified ordinary shuttle-box: rectangular acrylic plastic box with electrified grid floor, divided by low (10 cm) partitions - not in two as is customary, but three identical (20x30x30 cm) compartments. The sources of conditioned sound signals - tone (500 Hz) and click (100/min) were mounted on the side walls of the lateral compartments. At free access from the central compartment to any of the lateral ones - the device is adapted for the integration of two CRAAs; by means of a partition, blocking the access from the central compartment to any of the lateral ones turns the device into a common shuttle-box in which two consecutive CRAAs are elaborated before the integration procedures

Using the combination of left lateral-central compartments, the animals learn in response to 5 sec isolated action of conditioned signal - tone to jump from the central to lateral compartment; at the absence of avoidance reaction to conditioned stimulation an unconditioned painful - electric cutaneous stimulation of the paws is added till the jumping-escape is performed. On every experimental day 20 such presentations are carried out at 1 min intervals. An avoidance response to the presentation of only the conditioned signal was considered to be a correct response. The elaboration of CRAA was fulfilled until the attainment of a criterion level of learning by the animal - 85-100% of correct responses with its consecutive fixing during several days.

Then, according to this scheme the second CRAA was elaborated in this animal to the second conditioned signal - a click, using another combination of compartments of the device - central and right lateral ones.

After this, in conditions of free access from the central compartment to any lateral ones the procedure of the integration of two CRAAs was conducted. The animal was placed in the central compartment and during one experiment both conditioned signals were presented with 30 sec intervals in random order, according to the scheme by Gellerman (1933). On each experimental day 20 signals were presented. The task of correct response - jumping to the compartment appropriate to the conditioned signal - in such a situation of integration with an uncertain time of signal presentation appears to be absolutely unrealizable for the animal. While elaborating the given method [9] out of hundreds of animals subjected to such a procedure with uncontrolled situation none of these animals managed to exceed the random level of CRAA fulfillment. Over 20-25 sessions of such psychogenic stress (absence of pragmatic information), with vain attempts to find a correct solution, a pronounced steady pathological state - information neurosis - develops.

The assessment of emotionality and motor activity was fulfilled according to Hall's method of the open field.

The number of crossed squares, penetration into the centre, vertical stayings, the number and duration of grooming reactions, the number of explored holes, head raisings, urinations, defecations and boluses in the latter were registered during 5 min. Total data on horizontal and vertical activity was considered as an index of overall motor activity.

The results of additional assessment of emotionality according to modified test of proconflict situation of Vogel are presented in a separate communication.

The results were processed for mean values and statistically estimated according to Student's test.

The investigation of the behavior of each out of 5 generations was carried out in the following sequence: 1. Assessment of the initial status in the open field (and additionally according to Vogel's test); 2. Elaboration of the first CRAA during 10 days - a procedure which was used both as the test of stress-reactivity and for analysis of the learning performance itself. The data of our investigations on learning will be presented in a separate communication; 3. Assessment of the status in the open field 10 days later after elaboration of the first CRAA; 4. Consolidation of the first and elaboration of the second CRAA (with additional assessment of the emotionality according to the tests in the open field and Vogel) with their subsequent integration according to the above-described method for the development of information neurosis; 5. Sibling cross-breeding.

THE RESULTS. The investigation of the peculiarities of the behavior of the offspring of each of 5 generations in the open field began after attainment of puberty and was carried out according to a common scheme for all. First of all the level of motor activity and defecation in an initial status, i.e. before any experimental actions, was assessed. Then these indices were reestimated for the determination of stress-reactivity by means of second testing in the open field immediately after to exposure of moderate stress. According to the above-described methods a 10-day episode of the procedure of CRAA elaboration was considered to be a moderate stress (200 presentations).

The first testing revealed a progressive – from generation to generation – enhancement of motor activity of the offspring (Fig. 1,A). The activity of the F2-F5 offspring authentically exceeds ($P<0.01$) that of F1. So, the initial activity of the F2-F3 offspring exceeded that of F1 by 52% and 47%, respectively; the activity of F4 exceeded that of F1 by 107% as well as F3 preceding it by 39%. Although the motor activity of F5 was lower than of F5, it exceeded that of F1 by 52%.

Testing moderate stress action (10-day of CRAA elaboration) sharply suppresses motor activity in the open field of all generations except the first one (Fig. 1, B). So, post-stress activity of F2-F5 totals 48.5% in the initial state and 40.3% (correspondingly) in F2 and F3 offspring and 16% in F4 (the most sharp suppression). Post-stress suppression of the activity of F5 offspring was lower than that of those in F2-F4, but at the same time significantly exceeded the changes in F1. After a moderate stress the motor activity of F1 practically does not change, showing only a weak tendency to increase.

An incomparable great range of indices of initial and post-stress activity and a large scale of motor component of behavioral stress response of the F2-F5 offspring as compared to those in F1 (Fig. 2) claim attention.

In the initial status of the offspring of all the generations, side by side with a parallel above-described enhancement of motor activity, the percentage of the animals having a defecation in the open field increases from generation to generation (Fig. 3, A, solid curve). At the same time, their percent for every one of them out of

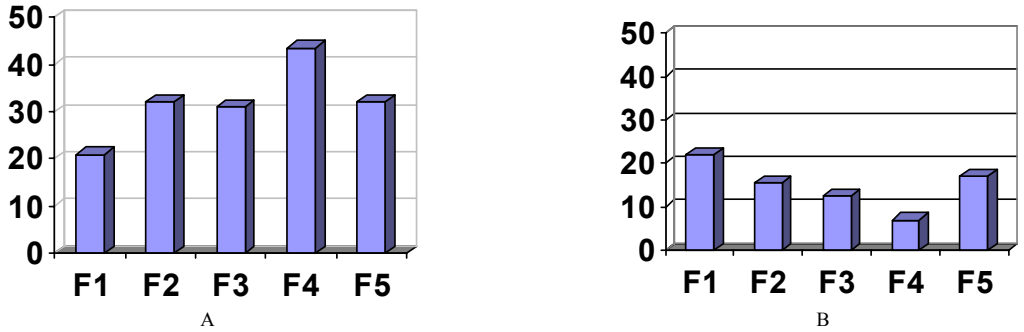


Fig. 1 A, B - Overall exploratory activity of the offspring of different generations in the open field.
A - Initial state before the beginning of the experiment;
B - After a moderate stress (bilateral active avoidance acquisition).
Comparison with exploratory activity of the first generation.

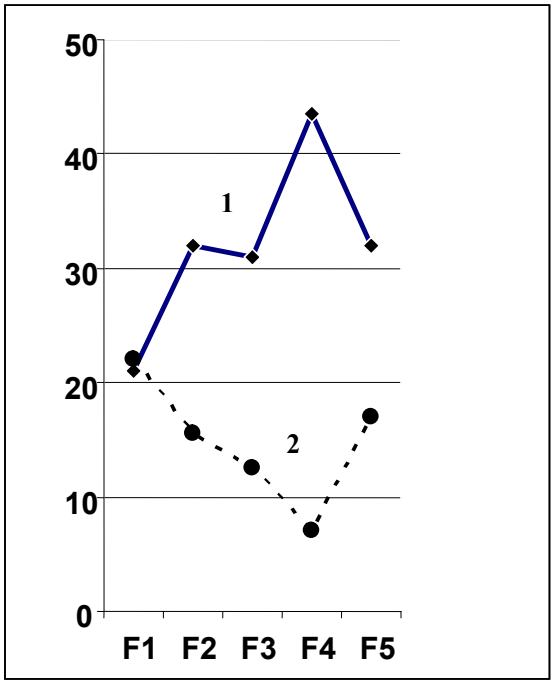


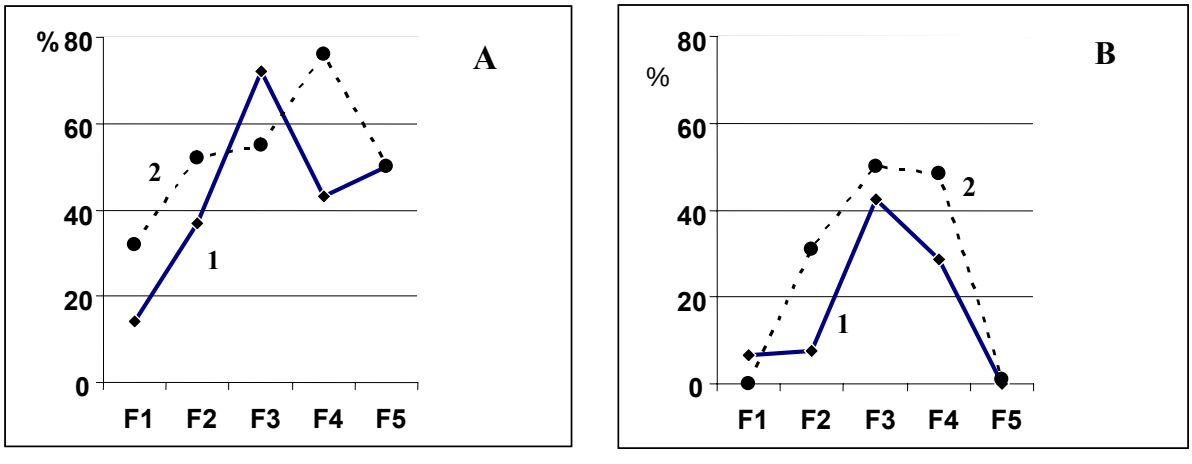
Fig. 2. Comparative dynamics of open field indices of overall exploratory activity of the offspring of different generations: 1 - initial state before the beginning of the experiment; 2 - after a moderate stress (bilateral active avoidance acquisition).

all the F2-F5 generations reliably exceeds those of F1 ($P<0.01$). These animals make 14.3% - in F1, 37% - in F2 and 72% -in F4 out of the total number of rats. Correspondingly, the percent of the animals having 5 and more fecal boluses in the open field increases (Fig. 3 B, solid curve). A difference was also observed in the quantity of boluses between the species of each generation.

After a moderate stress the percent of animals having defecation in the open field increases in all the generations, but the increase was most significant in F2-F5 (Fig. 3 A, dash line). Post-stress indices of defecation of F1, F2 and F4 significantly exceed those in the initial status, except F3 and F5, but at the same time, their index of defecation considerably exceeded that of F1. Along with this, the percent of the animals in F2, F3 and F4 having 5 and more boluses in defecation increases (Fig. 3, B, dash line).

Discussion. On the whole, the testing of behavior in the open field before and after a moderate stress in 5 generations of adult offspring of rat-parents with experimental information pathology of behavior has revealed the following peculiarities: 1) combination of high motor activity with a high level of defecation in the initial status of all the generations, except the first; 2) a sharp decrease of motor activity and still greater increase of the defecation level after a moderate stress in the offspring of all the generations, except the first; 3) a progressive growth of the degree of all said changes from generation to generation, with its peak in the offspring F4.

In animals of the first and direct progeny of the initial 8 parent pairs with information pathology of behavior in the initial status the least levels of motor activity and defecation are revealed as compared to F2-F5. Their reaction to a moderate stress shows in a fairly pronounced increase of defecation, reflecting an increase of emotional tension and fear, not accompanied by any considerable changes in locomotion. The latter reveals



A B

Fig. 3 A, B. Indices of excretory function of different generation offspring in the open field: 1 - in the initial state before the beginning of the experiment; 2 - after a moderate stress (bilateral active avoidance acquisition). A - percent of the offspring in each generation having defecations in the open field; B - percent of the offspring of each generation having 5 and more boluses in the open field.

only a slight tendency to increase. According to vegetative and motor indices, their stress response is incomparably small as compared to that in F2-F5 and could be considered as a sufficiently adequate reaction of the animal to stress, with a moderate increase of fear emotion. Therefore, the first generation of the offspring should be assessed as the most stress-resistant and stable as compared to the subsequent generations.

The offspring of all the consecutive generations have a similar type of peculiarities of motor behavior and excretory function in the initial status as well as an identical type of reaction to stress.

Their sharply increased initial motor activity - as compared to the stable F1 - as well as more pronounced degree of its change in post-stress state and as a result the incommensurably greater scales of the motor component of behavioral response to identical stress stimulation as compared to F1 are doubtless indices of a high level of excitability and its low threshold, high stress-reactivity, lability and correspondingly a high emotionality in the initial status of the F2-F5 offspring.

This is also corroborated by a high level of their defecation during the first testing in the open field. Defecation is a stable index of emotionality, according to Broadhurst and Bignami [10] and in Wimbey and Denenberg's opinion [11], namely it is defecation that specifically reflects the level of fear and alarm/anxiety in rats. However, according to the results of the present investigation, with the offspring of stressed rat-parents high motor activity may also be an index of high emotionality. The unusual correlation of two signs of emotionality in the open field in the animals of F2-F5 well agrees with the existent interpretation of data obtained by this method.

The behavior of animals in the open field is considered to be a dynamic balance of two competitive motivations: (a) the striving for the exploration of new territories, inherent in rodents and (b) fear characteristic of nocturnal animals in the face of the unknown and well lighted and sonically treated space. The level of motor-exploratory activity and defecation in the open field reflects the level of emotionality and fear of the animal under study. At the same time, as shown by genetic investigations of Hall [12] and Broadhurst et al. [10, 13, 14], a close reverse correlation between these signs occurs and, as a rule, low motor activity is combined with high defecation in high-emotional animals and, on the contrary - high motor activity and low defecation in less emotional animals. However, this rule is kept not always, as shown by the above-mentioned investigations of Broadhurst et al. [10, 13, 14] and works of other researchers [5, 11, 15]. The usual, reverse correlation of these two signs may change under certain conditions of experimentation and primarily in such cases when the animals were subjected to stress under the influence of strong or long-lasting factors [5, 10, 11, 13, 15] or if they were the offspring of female rats with pharmacological or surgical blockade of the hypophyseal-adrenal system [5]. While testing (especially during the first one) such animals in the open field, an increased emotion of fear may be reflected - along with an increase of defecation - not in a decrease but, on the contrary, in an increase of motor activity, which is interpreted as an increase of exploratory-oriented behavior or, more often, a combination of fear and attempts to escape [5, 10, 11, 13-15]. The results of these investigations warranted the conclusion [10, 12, 14, etc.] that the link of locomotion and excretory function (defecation) is determined by a complex polygenic structure, whose elements may be broken under certain conditions (stress, extreme impact), being conditioned either by the existence of variants of this system or variants of its functioning.

The fact that, under definite conditions, an increased motor activity may become an index of high emotional tension is observed precisely in our experiments. However, the most important is the fact that signs of post-stress state of animals described in the above-cited works are found in our experiments in the F2-F5 offspring in their initial, before-stress status before any special experimental exposures and which thus reflect the effect of parent-stress on the offspring.

A mild procedure of testing the animals in the open field only reveals their preceding background state of high emotional tension, i.e. they are permanently in the state of emotional stress of a definite degree: high excitability and its low threshold, high anxiety with motor restlessness (increased motor activity), increased tension of vegetative function (high defecation), increased reactivity, as a result of which a moderate stressor (procedure of 10 day elaboration of CRAA) evokes a great response, unequal to its force as compared to the stress-resistant stable F1 animals. In its aggregate of signs this state is similar to the described syndrome of chronic psychoemotional tension with expressed anxiety and well studied according to their psychophysiological and biochemical determinants [16, 17].

Thus, it may be said that the offspring (except the first generation) of rat-parents with chronic psychogenic stress in its initial state have specific features of parent pathology, in other words, they bear an imprint (trace) of parent pathology. It is important to point out that this anomalous state of emotionality of the F2-F5 offspring, as compared

to the stable F1 animals, far from worsening their learning performance, on the contrary, improved it (in terms of the rate of CRAA formation), which progressively increased from the third to the subsequent generations (details will be presented in a separate report). Judging by the character of the imprint of parent pathology on the F2-F5 offspring, one may speak of the high reliability of the model of Khananashvili and Domianidze used by us to develop experimental chronic information psychogenic stress. As already noted, one of the leading emotiogenic factors in this model is that of noncontrollability by the animals of the situation due to a deficiency of pragmatic information, conditioned by the random character of presentation of signal stimuli (see methods), i.e. the factor of unpredictability and uncertainty. **The particular** importance of unpredictability of signal stimulus in the activation of CNS factors, its expectations and discrepancy with the real effect is well documented by psychophysiological and electrophysiological studies of Lindsley (1960), Hernandez-Peon (1969), Haider (1970), Naatanen (1970), E. Sokolov (1970), and others. A particular strong activating impact of the factor of unpredictability on the endocrine adaptive systems has been already pointed out by Mason (1968), which was corroborated by modern interdisciplinary investigations. It has been shown that it is noncontrollable psychogenic stress and only with an active strategy of the animal's behavior that leads to stable disturbances both in the behavior and regulation of the hypophyseal-adrenal system [18].

Under anxiety and the syndrome of chronic psychoemotional tension an increased content not only of corticosteroids in the blood but of the main biochemical implementers of stress - catecholamines, growth hormone, and prolactin [16, 17, 19-21] - is observable. Intensification of ACTG secretion (determining the activation of the hypophyseal-adrenal system) as well as of prolactin takes place at the expense of increased metabolism and decrease of noradrenaline and dopamine concentrations in the hypothalamus [22]. Decrease of serotonin concentration in the hypothalamus also takes place.

The development of affective disorders induced by stress, such as anxiety and depression, is connected with the disturbance of the balance both in the hormonal and neuromediatory links of the common adaptive mechanism [16, 23-26].

Along with this, according to modern views, both the hormones and neuromediators constitute one of the main channels of influence on the activity of the genetic apparatus not only during its embryonic development but at all stages of ontogenesis [1, 2, 27]. At the same time, as is known, unlike neuromediators and peptide hormones which need secondary messengers to transmit a biological signal to the genome, steroid hormones, after binding with their cytosolic receptors, can be directly translocated into the nucleus and interact straightforward with chromatin. Thus, corticosteroids via a direct way, and meuromediators via the system of secondary cellular messengers (cyclic nucleotide-calmodulin-dependent proteinkinase) regulate the activity of the genome. The changes in gene expression induced in this way by the stress hormones, with corresponding reconstructions of cellular metabolism and neoplastic processes, provide for the flexibility of animal behavior, on the one hand, and via reproduction of cellular structures they can be transmitted and fixed in the generations and syngenesis, on the other [1-3, 16]. By naming this form of heredity as signal, M.E. Lobashev [3] emphasized its greater dynamism as compared to the generative (of heredity proper).

Conclusions.

1. The pronounced chronic psychogenic stress of rat-parents induces substantial changes in the behavior of their offspring due to: increased emotionality and anxiety, accompanied by increased locomotion and increased excretory function, increased excitability and its low threshold, high stress-reactivity and large stress response inadequate to the strength of stimulation.

2. These changes in behavior increase progressively from the second to subsequent generations of 5 continuous lines of the offspring.

3. The first generation of stressed rat-parents offspring does not reveal any substantial changes in behavior.

ადამიანისა და ცხოველთა ფიზიოლოგია

გენეტიკურად დაკავშირებული თაობების ვირთაგვების რიგში განმეორებული ქრონიკული ფსიქოგენური სტრესის გავლენა შთამომავლობის ქცევის ტიპოლოგიურ თავისებურებებზე. ემოციურობა, ლოკომოცია, სტრეს-რეაქტიულობა

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(წარმოდგენილია აკადემიკოს თ. ონიანის მიერ)

საწყისი 8 წყვილი ვირთაგვა-მშობლის 5 თანმიმდევრული თაობის შთამომავლობის 370 ზრდასრულ ნაშიერში, რომლებიც შეჯვარებული იყვნენ ძლიერი ფსიქოგენური სტრესის მდგომარეობაში (ინფორმაციული ნევროზი), ღია ველის პირობებში შესწავლილია მათ საწყის სტატუსში ემოციურობის (დეფეკაციის და მოტორული აქტიურობის) მაჩვენებლები, ე.ი. რაიმე ექსპერიმენტული პროცედურის ჩატარებამდე, აგრეთვე ზომიერი სტრესის (ორმხრივი აქტიური განრიდების პირობითი რეფლექსის გამომუშავება). დადგენილია, რომ ვირთაგვა-მშობლების ქცევის გამოხატული ინფორმაციული პათოლოგია არსებით ცვლილებებს იწვევს მათი შთამომავლობის ქცევაში, რაც გამოიხატება: გაზრდილ ემოციურობაში გამოხატული შფოთვით, რომელსაც თან სდევს მომატებული ლოკომოცია და ექსკრეტორული ფუნქცია, გაზრდილ აგზნებადობაში და მის დაბალ ზღურბლში, მაღალ სტრეს-რეაქტიულობაში და დიდ სტრესულ პასუხში, რომელიც არაადეკვატურია ზემოქმედების ძალის მიმართ. აღნიშნული ცვლილებები პროგრესულად იზრდება შთამომავლების უწყვეტი ხაზის მეორე თაობიდან შემდგომ თაობებამდე. სტრესირებული ვირთაგვა-მშობლების პირდაპირი შთამომავლების პირველი თაობა არ ავლენს რაიმე არსებით ცვლილებებს ქცევაში.

მიღებული შედეგები განიხილება ღია ველში ემოციურობის ნიშნების ურთიერთკავშირის ხასიათის შესახებ არსებული წარმოდგენების ასპექტში, აგრეთვე სტრესით გამოწვეული ინდუცირებული აფექტური დარღვევების ფორმირების შესაძლო გზებისა და შთამომავლობის აპარატზე მათი ზემოქმედების გზების თვალსაზრისით.

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