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Reinforcing systems of the brain and quantification of their work

Petr D. Shabanov[1,2], Yan B. Likhtman[1], Andrei A. Lebedev[1]

[1] Institute of Experimental Medicine, Saint Petersburg, Russia;
[2] Kirov Military Medical Academy, Saint Petersburg, Russia

ABSTRACT

BACKGROUND: The reinforcing systems of the brain are represented by the ventral forbrain dopaminergic bundle, which innervates the emotiogenic structures of the limbic system. Their study shows the reproduction of unconditioned (self-stimulation, self-administration) and conditioned reflex (preference for place, temperature, color) reactions. The quantitative assessment of the brain's reinforcing systems remains unclear. For self-stimulation of brain structures, the change of the pedal presses in the Skinner chamber and some calculated coefficients are used, for example, the "mismatch coefficient", which characterizes the temporal characteristics of the pedal pressings.

AIM: To develop, test, and substantiate an additional objective quantitative method for assessing the reinforcing systems of the brain, called the "addiction coefficient", based on an analysis of the effect of three psychoactive compounds (amphetamine, morphine and ethanol) in different doses on self-stimulation of the lateral hypothalamus in rats.

MATERIALS AND METHODS: The main method for studying the reinforcing systems of the brain was the reaction of self-stimulation of the lateral hypothalamus in Wistar rats, which was modulated by the administration of psychoactive substances. The psychomotor stimulant amphetamine (phenamine) hydrochloride (0.5, 1, 2, and 4 mg/kg), narcotic analgesic morphine hydrochloride (1, 2, 4, and 8 mg/kg), and ethanol (0.5, 1, 2, and 4 g/kg) administered intraperitoneally were used as inductors of reinforcing. The control was the administration of of 0.9% NaCl solution (0.1, 0.2, 0.4, and 0.8 ml/rat).

RESULTS: The use of different controls, characterized by an increase or decrease in the self-stimulation reaction in response to the introduction of 0.9% NaCl solution, showed that calculated coefficients, including the "mismatch coefficient", can change in different directions and do not objectively reflect the reinforcing effects of pharmacological substances. The proposed "addiction coefficient", which reflected the component of psychic dependence, changed unidirectionally toward an increase. The degree of this increase can be tens and hundreds of percent of the control and is significantly independent of the initial values of self-stimulation. As expected, the "addiction coefficient" increased most clearly after amphetamine administration and less significantly after morphine and ethanol injections.

CONCLUSIONS: The "addiction coefficient" of a psychoactive substance, calculated as the ratio of the increase in pedal presses to the value of the "mismatch coefficient", is a clear quantitative indicator when assessing the reinforcing properties of psychoactive substances in the self-stimulation reaction of the lateral hypothalamus. The "addiction coefficient" does not significantly depend on the initial level of self-stimulation and is recommended for a comparative assessment of the reinforcing properties of primarily related psychoactive compounds.

Keywords: reinforcing systems of the brain; structural and functional organization; self-stimulation of the lateral hypothalamus; quantitative indicators; addiction coefficient; amphetamine; morphine; ethanol; pharmacological analysis; rats.

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Подкрепляющие системы мозга и количественная оценка их работы

П.Д. Шабанов[1,2], Я.Б. Лихтман[1], А.А. Лебедев[1]

[1] Институт экспериментальной медицины, Санкт-Петербург, Россия;
[2] Военно-медицинская академия им. С.М. Кирова, Санкт-Петербург, Россия

АННОТАЦИЯ

Обоснование. Подкрепляющие системы головного мозга представлены в основном вентральным передним дофаминергическим пучком, иннервирующим эмоциогенные структуры лимбической системы. Их изучение сводится к воспроизведению безусловных (самостимуляция, самовведение) и условно-рефлекторных (предпочтение места, температуры, цвета) реакций. Остаются нерешенными вопросы количественной оценки подкрепляющих систем мозга. Для самостимуляции мозговых структур используют прирост нажатий на педаль в камере Скиннера и некоторые расчетные коэффициенты, например «коэффициент рассогласования», характеризующий временные особенности нажатия на педаль.
Цель — разработка, апробация и обоснование дополнительного объективного количественного способа оценки подкрепляющих систем мозга, названного «коэффициентом аддиктивности», на основе анализа влияния трех психоактивных соединений (фенамина, морфина и этанола) в разных дозах на самостимуляцию латерального гипоталамуса у крыс.
Материалы и методы. Основным методом изучения подкрепляющих систем мозга была выбрана реакция самостимуляции латерального гипоталамуса у крыс Вистар, которую модулировали введением психоактивных веществ. В качестве индукторов подкрепления использовали психомоторный стимулятор фенамина (амфетамина) гидрохлорид (0,5; 1; 2; 4 мг/кг), наркотический анальгетик морфина гидрохлорид (1; 2; 4; 8 мг/кг) и этанол (0,5; 1; 2; 4 г/кг), которые вводили внутрибрюшинно. В качестве контроля вводили разные дозы 0,9 % раствора NaCl (0,1; 0,2; 0,4; 0,8 мл на крысу).
Результаты. Использование разных доз 0,9 % раствора NaCl в качестве контроля, вызывающих повышение или снижение реакции самостимуляции, показало, что расчетные коэффициенты, такие как «коэффициент рассогласования», также могут меняться разнонаправленно и объективно не отражать подкрепляющих эффектов фармакологических веществ. Предлагаемый нами «коэффициент аддиктивности», отражающий компонент психической зависимости, всегда меняется однонаправленно в сторону увеличения. Степень этого увеличения может составлять десятки и сотни процентов от контроля, причем существенно не зависит от исходных значений самостимуляции. Как и ожидалось, «коэффициент аддиктивности» наиболее наглядно возрастает после введения психостимулятора фенамина и менее значимо после инъекций морфина и этанола.
Заключение. «Коэффициент аддиктивности» психоактивного вещества, рассчитываемый как соотношение прироста нажатий на педаль к величине «коэффициента рассогласования», служит наглядным количественным показателем при оценке подкрепляющих свойств психоактивных веществ в реакции самостимуляции латерального гипоталамуса. «Коэффициент аддиктивности» существенно не зависит от исходного уровня самостимуляции и рекомендован для сравнительной оценки подкрепляющих свойств в первую очередь родственных психоактивных соединений.

Ключевые слова: подкрепляющие системы мозга; структурно-функциональная организация; самостимуляция латерального гипоталамуса; количественные показатели; коэффициент аддиктивности; фенамин; морфин; этанол; фармакологический анализ; крысы.

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BRAIN'S REINFORCEMENT SYSTEMS

The brain's reinforcement systems have been largely described by experimental data on self-stimulation responses reproduced by various structures of the limbic system, beginning in the mid-1950s. The reinforcing systems of the brain has undergone significant changes since its initial conceptualization. Initially, the autonomy of individual brain structures (e.g., the hypothalamus) was proposed, whereby self-stimulation was reproduced [1]. This has since evolved into a unified system of brain structures, which are innervated by the medial forebrain bundle [2], more precisely by a group (cluster) of dopaminergic axons. These structures originate in the ventral region of the midbrain and extend to various limbic system (Fig. 1).

Given that the axons of the medial forebrain bundle stimulate numerous brain structures, it was assumed that they were equally involved in reinforcement or the work of the brain's reinforcing systems. However, this hypothesis was modified to indicate that only a subset of these structures, initially described based on their morphological similarities, played a role in reinforcement. This subset, designated as the extended amygdala system, included the central nucleus of the amygdala, contiguous nucleus, nucleus of the bed of the terminal stripe, and substantia innominata [3]. Subsequently, these structures of the enlarged amygdala, or paraamygdalar complex, were regarded as the morphofunctional basis of reinforcement [4, 5]. Figure 2 presents a schematic representation of the paraamygdalar complex.

However, the conventional idea about the brain reinforcement systems, which are a group of brain structures innervated by the medial forebrain bundle (Fig. 3), remains well received, especially among specialists working with the brain self-stimulation response. This is because the response is reproduced from most of the structures innervated by axons in the medial forebrain bundle of the midbrain, which has approximately 50,000 neurons [7].

Reconstruction of the midbrain nuclei forming the medial forebrain bundle was performed in our laboratory [9]. It revealed that the structure of these nuclei is complex and that a simplified interpretation of both the bundle and its derivatives is unfeasible (Fig. 4).

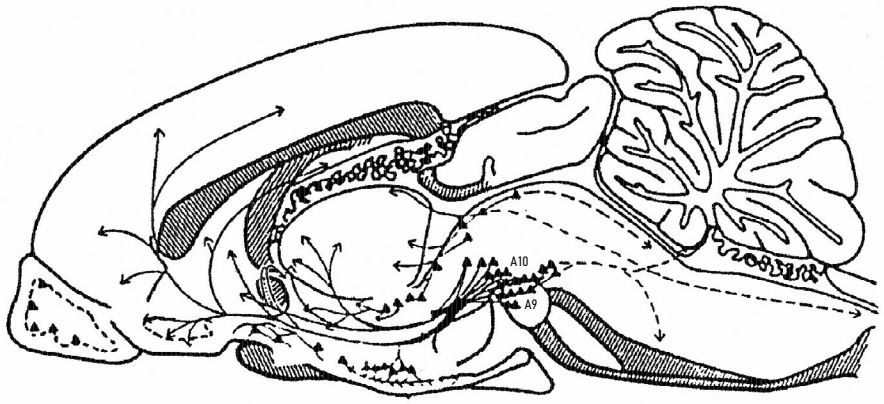

Fig. 1. Schematic representation of the mesocorticolimbic system of the rat brain. A9 and A10: the zones of location of the dopaminergic nuclei of the ventral tegmental area [2]

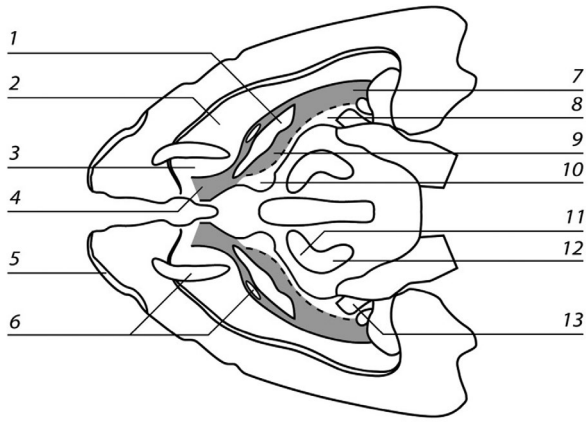

Fig. 2. Paraamygdalar complex structures (highlighted in dark) on a cross section of the rat brain: *1*, dorso-ventral pallidum; *2*, caudate nucleus-putamen; *3*, nucleus accumbens (core); *4*, nucleus accumbens (shell); *5*, lateral olfactory tract; *6*, anterior commissure; *7*, central nucleus of the amygdala; *8*, medial region of the amygdala; *9*, lateral nucleus of the bed of the stria terminalis; *10*, medial core of the bed of the stria terminalis; *11*, paraverticular nucleus of the hypothalamus; *12*, lateral hypothalamus; *13*, optic tract [6]

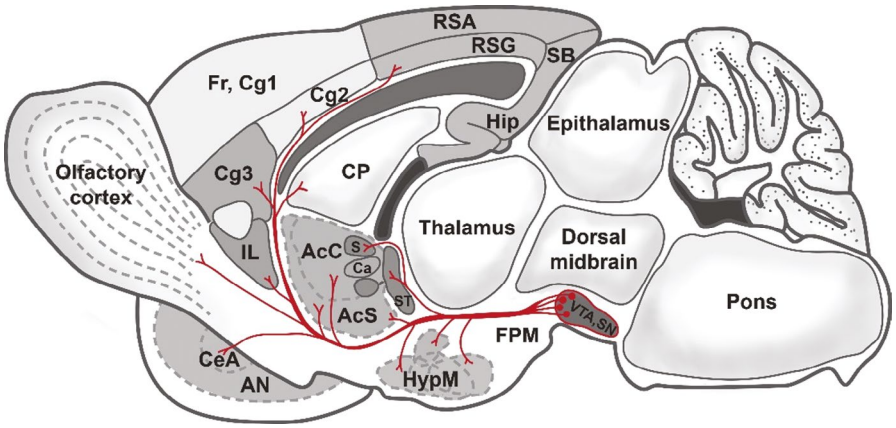

Fig. 3. Scheme of the main projection connections of the dopaminergic nuclei of the midbrain in rats [8]. VTA, SN, complex of ventral tegmental nuclei; VTA, ventral tegmental area; SN, substantia nigra of the midbrain; FPM, forebrain medial bundle; Pons, pons; Thalamus, thalamus; Dorsal midbrain, dorsal part of the midbrain; Epithalamus, epithalamus; HypM, hypothalamus medial; AcC, central part of the nucleus accumbens (core); AcS, nucleus accumbens cover (shell); S, septal nucleus; CeA, AN, complex of amygdala nuclei; IL, infralimbic field; ST, nucleus of the bed of stria terminalis; CP, globus pallidus; Olfactory cortex, visual cortex; Fr, Cg1, Cg2, and Cg3, anterior cingulate areas; RSA and RSG, retrosplenial cingulate areas; Hip, hippocampus

BRAIN SELF-IRRITATION

Most studies on the morphofunctional organization of the brain reinforcement systems have been obtained using the self-stimulation response. As previously stated, self-stimulation is reproduced from numerous structures of the limbic system of the brain that determine an organism's emotional–motivational activity. In experimental conditions, self-stimulation is most often reproduced from the lateral nuclei of the hypothalamus. For example, in an experiment using a Skinner box, self-stimulation is characterized by high reproducibility, stability, reliability, and a sufficiently high level of pedal clicks, indicating the quantitative characteristics of the self-stimulation reaction.

The brain's self-stimulation reaction is used to examine unconditional reinforcement, considering that no conditioned reflex mechanisms are involved in the realization of self-stimulation. However, the animal's activity in a Skinner's box is regarded as an instrumental reflex. The reveals that brain tissues specifically react to electric current, eventually forming a motor act (in a Skinner's classical box, this is pressing the pedal). The direct quantitative characteristics of the self-stimulation reaction are used for assessing physiological or pharmacological effects. The characteristics include the number of pedal presses (absolute and relative) and the increase in pedal presses after the introduction of psychoactive agents or the decrease in pedal presses when introducing depriming agents. Additionally, the indicators of the sensitivity of brain tissue to the effect of the current are determined by the current threshold, which causes the expected motor reaction. This reaction is commonly observed as pedal pressing. Importantly, the current thresholds causing self-stimulation (measured in microamperes) exhibit considerable variability between animals, due to minor variations in the localization of electrode tips in the hypothalamus and gradual formation of connective tissue bags in the electrode area following the prolonged use of an animal with electrodes implanted in the brain (>1–1.5 months). Grigoryan [10], from the Institute of Higher Nervous Activity and Neurophysiology, USSR Academy of Sciences, Moscow, proposed the determination of a specific mismatch coefficient, which allowed for the consideration of the behavioral characteristics of rats in Skinner pedal boxes. This coefficient is calculated using a specialized formula that considers the duration of pedal pressing and the time of the beginning and end of stimulation (Fig. 5).

$$K = (T_1 - T_2) / (T_1 + T_2),$$

where K is the mismatch coefficient, T_1 is the time of pedal pressing after the end of stimulation in case of prolonged pressings of duration >0.4 s, and T_2 is the time from the moment of pedal release to the end of stimulation.

The mismatch coefficient is from –1 to +1 and indicates the proportion of activation of the positive and negative reinforcing phases of self-stimulation [12, 13]. A positive coefficient indicates that the rat continued to press the pedal after the brain stimulation stopped, whereas a negative mismatch coefficient shows that the rat stopped pressing the pedal before the brain stimulation stopped. The need for introducing the mismatch coefficient is conditioned by the theoretical ideas that the self-stimulation response can be considered as a simultaneous activation of positive and negative reinforcement mechanisms or as a "difference in the emotional gradient" from negative to positive [14]. The shift toward increasing and decreasing coefficients determines the changes in both the frequency of self-stimulation and reinforcing properties of the brain. Therefore, as an additional

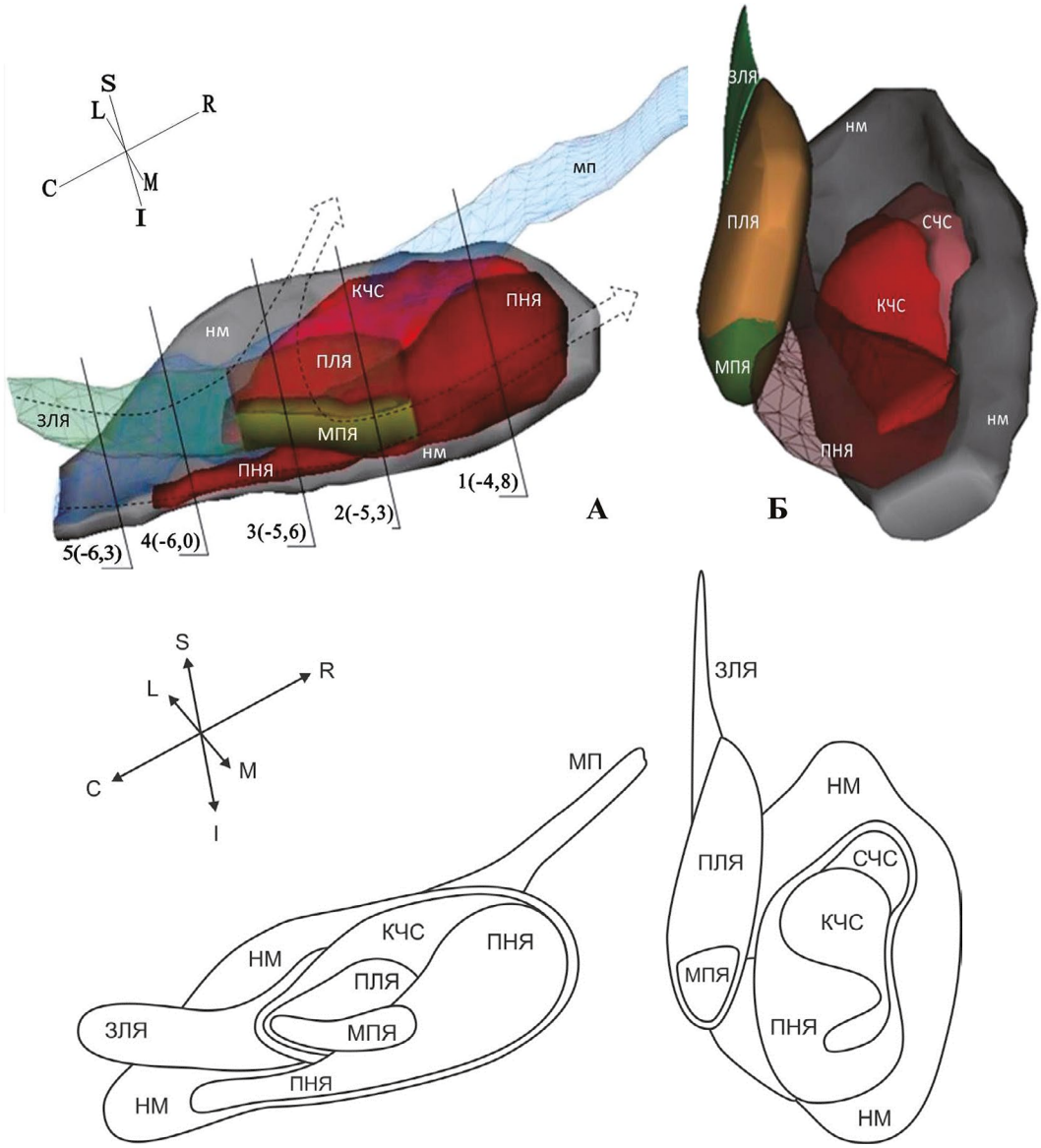

Fig. 4. Topographic location of the dopaminergic nuclei of the midbrain tegmentum based on the morphological reconstruction of the nuclei of the ventral tegmental area and substantia nigra (top) and their schematic representation (bottom) according to Droblenkov. A, medial projection; Б, anterior projection. Nuclei of the ventromedial tegmentum of the midbrain: ПНЯ, paranigral nucleus; ПЛЯ, anterior linear nucleus; ЗЛЯ, posterior linear nucleus; МПЯ, interfascicular nucleus. Dopaminergic nuclei of the ventrolateral tegmentum: КЧС, compact part of the substantia nigra; СЧС, reticular part of the substantia nigra. White matter: нм, cerebral peduncle; мп, medial lemniscus. Axes directions: C-R, caudo-rostral; M-L, medio-lateral; S-I, superior-inferior. Dotted line: trunk of the medial forebrain bundle (ventral: to the cingulate cortex and nucleus accumbens; dorsal: to the striatum) [9]

criterion for changes in the reinforcing properties of self-stimulation, the mismatch coefficient is used for evaluating the effect of pharmacological drugs, as demonstrated in several studies [4–8]. Hence, we included the calculation of the mismatch coefficient in the self-stimulation data processing program and to calculate it automatically, i.e., to automate and objectify the whole range of behavioral changes in rats during self-stimulation.

However, both indicators of self-stimulation study (i.e., changes in the number of taps and mismatch coefficient) are often insufficient because they can change in different directions and thus the expected results, i.e., when

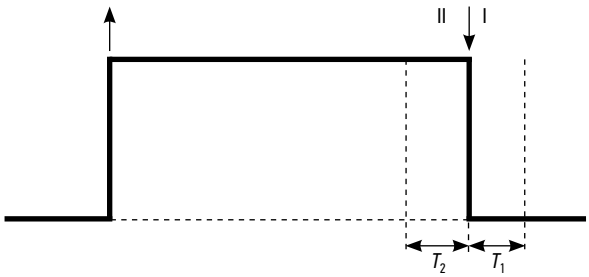

Fig. 5. Diagram illustrating the calculation of the "mismatch coefficient". I and II are the moments of pedal depressing. Arrows indicate the beginning and end of stimulation

the number of taps increases (activation of reinforcing systems), a decrease in the mismatch coefficient is most often registered. Moreover, an increase in the number of taps is possible, which would result in a unidirectional change of indicators. In such cases, drawing a definitive conclusion about the activation or depression of the brain reinforcement systems is challenging. This implies that one of the indicators (more often the mismatch coefficient) is not considered, and the other is emphasized more. Furthermore, the addictive potential of psychoactive substances, such as psychostimulants and opiates, cannot be accurately determined by solely considering these two parameters. The indices obtained when psychostimulants (e.g., amphetamine, phencyclidine) are administered consistently are greater than those observed after the administration of morphine, fentanyl, diacetylmorphine, and other narcotic analgesics [15].

Attempts have been made to introduce additional indicators for assessing self-stimulation responses. A reasoning involved the isolation or calculation of an addictiveness index, which could be used to assess the drugogenic potential of a substance. This procedure is crucial in the preclinical study of psychotropic substances. The fundamental principle was to use doses of psychoactive substances that produced comparable effects [16]. However, this approach has not been consistently effective when comparing, for example, diacetylmorphine (heroin) to ethanol regarding excipotential doses that could lead to the activation of reinforcing systems and potential dependence. In the first case, the concentration will be relatively low (5–10–20 mg/kg), whereas in the second case, it will be significantly higher (>4 g/kg), which indicates intoxication with the disruption of all behavioral responses. Consequently, such an indicator is not consistently objective, as the calculated equivalent doses of substances may be exceedingly high compared to the reference (in this case, it is crucial to select a reference substance or a comparison drug) and potentially result in more adverse effects than the actual impact on the reinforcing systems of the brain.

ADDICTIVENESS COEFFICIENT

We analyzed the effects of phenamine, morphine, and ethanol on self-stimulation of the lateral hypothalamus in rats to develop and validate an additional objective quantitative method for assessing the activation of brain reinforcement systems (an indicator of addictiveness).

Self-stimulation of the lateral hypothalamus was investigated in 78 male Wistar rats weighing 200–220 g placed inside standard plastic cages with vivarium conditions in groups of five. The animals were housed at the Institute of Experimental Medicine and maintained under inverted light conditions between the hours of 08:00 and 20:00, with an air temperature of 20°C–22°C and a relative humidity of 50%–70%. They had free access to water and food. Traditional brain self-stimulation, in the form of pedal self-stimulation in Skinner's box, was used.

Electrodes were implanted into the brains of rats under nembutal anesthesia (50 mg/kg) using a stereotactic device (Medicor, Hungary). The electrodes were constructed from nichrome and insulated in glass. The diameter of the electrode was 0.25 mm, the length of the bare tip was 0.25–0.30 mm, and its thickness was 0.12 mm. They were implanted bilaterally into the lateral hypothalamic nucleus at the following coordinates: AP = 2.5 mm posterior to the bregma, SD = 2.0 mm lateral to the sagittal suture, and H = 8.4 mm from the skull surface [17].

An electrode of indifferent composition, constructed from nichrome wire, was attached to the skull of the animal. The electrodes were connected to a microconnector fixed to the skull with self-hardening plastic.

Ten days after electrode implantation in the brain, rats were trained to press a pedal in a Skinner box for electrical stimulation of the brain. This stimulation involved rectangular pulses of negative polarity of 1 ms duration with a frequency of 100 Hz for 0.4 s. The current thresholds were set in the fixed bundle mode. For repeated stimulation, the animal was forced to press the pedal again. The frequency and duration of presses were recorded automatically. The mismatch coefficient was calculated according to the previously described methodology. On experiment day three, pharmacological preparations were initiated after the reaction reached a stable current strength. The number of pedal presses and mismatch coefficient were recorded for a 10-min interval; then, an intraperitoneal injection of the drug was performed. After 30 min, the same parameters were recorded for a 10-min interval. Furthermore, the addictiveness coefficient was calculated as the ratio of the increase in the number of pedal presses to the mismatch coefficient, which was expressed in conventional units.

At the end of all experiments, morphological control of electrode tip localization was conducted on a series of frontal brain slices, which were stained according to the Nissl method. Prior to this, coagulation through the implanted electrodes with 1 mA current for 30 s was performed.

The following were used for pharmacologic analysis and were administered intraperitoneally:

1) Isotonic sodium chloride solution (control: 0.1, 0.2, 0.4, and 0.8 mL per rat)
2) Psychomotor stimulant phenamine (amphetamine) hydrochloride (0.5, 1, 2, 2, and 4 mg/kg)
3) Narcotic analgesic morphine hydrochloride (1, 2, 4, and 8 mg/kg)
4) Ethanol (0.5, 1, 2, and 4 g/kg)

The statistical processing of the obtained quantitative data was conducted using GraphPad Prism v.6 software. Data were presented as mean ± standard deviation. The significant differences between groups were determined using one-factor ANOVA analysis of variance. For comparison

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between two groups, the Student's *t*-test for independent samples was used.

Analysis of the effect of different doses of phenamine on self-stimulation of the lateral hypothalamus (Table 1) revealed a dose-dependent increase in the number of pedal presses, with a 33% increase observed after administration of 0.5 mg/kg and a 66% increase after administration of 4 mg/kg. Concurrently, the mismatch factor decreased from 0.60 to 0.34. Data indicate that phenamine activates the brain's reinforcement systems. However, the most significant findings were those related to the addictiveness coefficient, which demonstrated a gradual increase from 2.22 ± 0.03 (0.5 mg/kg) to 4.88 ± 0.09 (4 mg/kg). In comparing control I (1.15 ± 0.02) to control II (1.12 ± 0.05), the results demonstrated that the reinforcing systems of the brain become increasingly involved as the dose of psychostimulant increases. Two control groups were included in the study: one (I) exhibited a 10% increase in the number of taps and the other (II) demonstrated a 9% decrease in this index following the administration of 0.9% NaCl solution.

The choice of two control groups was attributed to experiments with self-stimulation, which consists in the fact that one animal (rat) is used in the experiment repeatedly. When including an animal in the experiment, electrodes are implanted in the brain for a long period (in our experiments, at least 1–1.5 months). Following the 10-day quarantine period, the rat is trained to press the pedal to receive electrical stimulation (reinforcement) for 3–4 days. This is done until the self-stimulation response of the lateral hypothalamus stabilizes.

Subsequently, before the administration of the pharmacological substance, control values of self-stimulation were recorded in each rat for 10 min. Thereafter, the pharmacological substance was administered, and self-stimulation reaction was recorded again in 30 min for a 10-min interval. The effect of the substance was compared with the data of control testing (before substance administration). The administration of pharmacological substances was repeated with a 4–5-day interval. Each rat was used repeatedly, with a 4–5-day break between administration and testing. Thus, each rat was tested at least 7–10 times (7–10 sessions), and the results of all sessions with administration of a particular pharmacological substance were statistically calculated.

Table 1 reveals that control groups I and II diverge in the directionality of the effects of repeated testing. In the case of control group I, self-stimulation increased by 10%, whereas in the case of control group II, self-stimulation decreased by 9%. The mismatch coefficients in control group I remained relatively stable, decreasing by only 5% from 0.21 ± 0.02 to 0.20 ± 0.01. The calculated addictiveness coefficient, defined as the ratio of the increase in the number of pedal presses to the mismatch coefficient in control group I, was 1.15 ± 0.02. In contrast, control group II initially exhibited a slight (–9%) decrease in self-stimulation, followed by a significant 19% decrease in the mismatch ratio from 0.31 ± 0.03 to 0.25 ± 0.05. The addictiveness coefficient was found to be 1.12 ± 0.05, which was not significantly different from the result observed in control group I. This indicates that, regardless of the direction of change in the number of pedal presses (increasing or decreasing), the addictiveness coefficient remained relatively stable.

A different scenario emerged when morphine was studied in relation to self-stimulation of the lateral hypothalamus (Table 2). Two control groups were also selected for comparison with the effects of the drug. One of these (group I) exhibited a slight increase in the number of pedal presses (+10%), and the other exhibited a decrease in this index (–6%). The mismatch coefficient in control group I

Table 1. Effect of amphetamine at different doses on the assessing of the lateral hypothalamus in rats

Substance, dose	Number of pedal presses per 10 min (%)		Mismatch coefficient, relative units		Addictiveness coefficient, relative units
	before	after	before	after	
Control group I (0.9% NaCl solution)	147 ± 16	161 ± 12 (1.10 ± 0.08)	0.21 ± 0.02	0.20 ± 0.01 (0.95)	1.15 ± 0.02
Control group II (0.9% NaCl solution)	156 ± 13	142 ± 19 (0.91 ± 0.12)	0.31 ± 0.03	0.25 ± 0.05 (0.81)	1.12 ± 0.05
Phenamine 0.5 mg/kg	245 ± 33	325 ± 23$^{*\$\#}$ (1.33 ± 0.09)	0.15 ± 0.03	0.09 ± 0.02$^{*\$\#}$ (0.60)	2.22 ± 0.03$^{*\$}$
1 mg/kg	234 ± 17	322 ± 29$^{*\#}$ (1.38 ± 0.12)	0.25 ± 0.05	0.11 ± 0.02$^{*\$\#}$ (0.44)	3.14 ± 0.05$^{***\$\$\$}$
2 mg/kg	214 ± 16	307 ± 23$^{*\$\#}$ (1.43 ± 0.11)	0.21 ± 0.04	0.12 ± 0.03$^{*\$\#}$ (0.57)	2.51 ± 0.05$^{**\$\$}$
4 mg/kg	203 ± 31	337 ± 26$^{*\$\$\#}$ (1.66 ± 0.13)	0.32 ± 0.10	0.11 ± 0.03$^{*\$\#}$ (0.34)	4.88 ± 0.09$^{***\$\$\$}$

Note: $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$ compared with control group 1; $^{\$}p < 0.05$; $^{\$\$}p < 0.01$; $^{\$\$\$}p < 0.001$ compared with control group 2; $^{\#}p < 0.05$ compared with values before drug administration.

increased by 4% from 0.23 ± 0.03 to 0.24 ± 0.04. Conversely, in control group II, the coefficient decreased significantly by 24% from 0.34 ± 0.03 to 0.26 ± 0.05. Consequently, the addictiveness coefficient in control group I was 1.06 ± 0.04 and 1.24 ± 0.07 in control group II.

The evaluation of morphine effects on self-stimulation depended on the initial control values. In control group I, the number of pedal presses when the drug was administered at a dose of 1–2 mg/kg was not statistically different from control values, increasing only when administered at doses of 4 mg/kg (+27%) and 8 mg/kg (+31%). In contrast, in control group II, all doses of morphine (1–2–4–8 mg/kg) were found to have a significant activating reinforcement effect on this index. The mismatch coefficient significantly decreased from 0.22 ± 0.02 to 0.13 ± 0.04 ($p < 0.01$) following the administration of 2 mg/kg morphine. This reduction was further pronounced at a dose of 8 mg/kg, with the mismatch coefficient reaching 0.16 ± 0.03. However, reinforcing system involvement in the brain is more evident in the calculation of the addictiveness coefficient, which exhibited a moderate increase with morphine administration at all doses (1–2–4–8 mg/kg), regardless of the initial values of control groups I (1.06 ± 0.04) and II (1.24 ± 0.05). Notably, the values of the addictiveness coefficient were not particularly high compared to the effect of phenamine, which ranged from 1.40 ± 0.07 to 2.00 ± 0.07.

Table 2. Effect of morphine at different doses on the assessing of the lateral hypothalamus in rats

Substance, dose	Number of pedal presses per 10 min (%)		Mismatch coefficient, relative units		Coefficient addictiveness coefficient, relative units
	before	after	before	after	
Control group I (0.9% NaCl solution)	166 ± 19	182 ± 12 (1.10 ± 0.09)	0.23 ± 0.03	0.24 ± 0.04 (1.04)	1.06 ± 0.04
Control group II (0.9% NaCl solution)	153 ± 12	144 ± 23 (0.94 ± 0.15)	0.34 ± 0.03	0.26 ± 0.05 (0.76)	1.24 ± 0.05
Morphine 1 mg/kg	211 ± 19	242 ± 18$^{\$}$ (1.15 ± 0.09)	0.28 ± 0.03	0.23 ± 0.06 (0.82)	1.40 ± 0.07$^{*\$}$
2 mg/kg	215 ± 21	247 ± 15$^{\$}$ (1.18 ± 0.11)	0.22 ± 0.02	0.13 ± 0.04$^{*\$\#}$ (0.59)	2.00 ± 0.07$^{**\$\$}$
4 mg/kg	203 ± 31	257 ± 13$^{*\$\#}$ (1.27 ± 0.06)	0.20 ± 0.03	0.18 ± 0.05 (0.90)	1.41 ± 0.06$^{*\$}$
8 mg/kg	178 ± 19	232 ± 25$^{*\$\#}$ (1.31 ± 0.14)	0.20 ± 0.05	0.16 ± 0.03$^{\$}$ (0.80)	1.64 ± 0.04$^{**\$}$

Note: $^{*}p < 0.05$; $^{**}p < 0.01$ compared with control group 1; $^{\$}p < 0.05$; $^{\$\$}p < 0.01$ compared with control group 2; $^{\#}p < 0.05$ compared with values before drug administration.

Table 3. Effect of ethanol at different doses on the assessing of the lateral hypothalamus in rats

Substance, dose	Number of pedal presses per 10 min (%)		Mismatch coefficient, relative units		Coefficient addictiveness coefficient, relative units
	before	after	before	after	
Control group I (0.9% NaCl solution)	141 ± 16	153 ± 14 (1.09 ± 0.12)	0.24 ± 0.02	0.22 ± 0.03 (0.92)	1.18 ± 0.04
Control group II (0.9% NaCl solution)	161 ± 11	145 ± 24 (0.89 ± 0.15)	0.14 ± 0.03	0.18 ± 0.06 (1.28)	0.70 ± 0.05
Ethanol 0.5 g/kg	156 ± 21	167 ± 17 (1.07 ± 0.11)	0.33 ± 0.11	0.21 ± 0.07$^{\#}$ (0.64)	1.67 ± 0.11$^{*\$\$}$
1 g/kg	135 ± 13	148 ± 20 (1.10 ± 0.15)	0.21 ± 0.02	0.14 ± 0.05$^{*\$\#}$ (0.67)	1.64 ± 0.07$^{*\$\$}$
2 g/kg	157 ± 14	192 ± 16$^{*\$\#}$ (1.22 ± 0.10)	0.25 ± 0.05	0.21 ± 0.12 (0.84)	1.45 ± 0.14$^{*\$\$}$
4 g/kg	148 ± 16	162 ± 12 (1.10 ± 0.08)	0.21 ± 0.02	0.20 ± 0.01 (0.95)	1.16 ± 0.03$^{\$}$

Note: $^{*}p < 0.05$; $^{**}p < 0.01$ compared with control group 1; $^{\$}p < 0.05$; $^{\$\$}p < 0.01$ compared with control group 2; $^{\#}p < 0.05$ compared with values before drug administration.

Assessing the impact of ethanol on the brain's reinforcing systems is more challenging (Table 3). Two control groups were included in the study, which exhibited an initial increase (+9% in control group I) or decrease (–11% in control group II) in the number of pedal presses following the administration of a 0.9% NaCl solution. The mismatch coefficient in control group I showed a moderate decrease of 8% from 0.24 ± 0.02 to 0.22 ± 0.03, whereas it presented a significant increase of 28% in control group II (from 0.14 ± 0.03 to 0.18 ± 0.06). Among the ethanol doses studied (range: 0.5–4 g/kg), only one (2 g/kg) resulted in a small increase in pedal presses (22%), although the mismatch coefficient exhibited a significant decrease following the administration of 0.5 and 1 g/kg. However, the proposed addictiveness coefficient was 1.18 ± 0.04 in control group I and 0.70 ± 0.05 in group II. The former was consistent with the data of previous experiments, in which the addictiveness coefficient ranged from 1.06 to 1.24, and the latter exhibited a notable discrepancy from the typical values, with an addictiveness coefficient of 0.70. Ethanol administration at a dose of 2 g/kg significantly increased the number of pedal presses relative to control groups I and II. Furthermore, the mismatch coefficient significantly decreased when the effect of ethanol administration at a dose of 1 g/kg was assessed, also relative to both control groups. The addictiveness coefficient showed a more pronounced increase following ethanol administration at doses of 0.5–1–2 g/kg relative to control group I and at all doses (0.5–1–2–4 g/kg) relative to control group II. Consequently, regardless of baseline control, the addictiveness coefficient remains the most feasible indicator of the activation of reinforcing systems by the self-stimulation response of the lateral hypothalamus.

Obtained data indicates that the addictiveness coefficient in all animal groups and all doses of psychoactive substances significantly increased, demonstrating the involvement of reinforcing systems in the brain in their action. The addictiveness coefficient can be easily calculated based on other quantitative indicators of self-stimulation of the lateral hypothalamus. It does not replace these indicators but takes them into account. It has a clear semantic content and specific and understandable numerical values.

Importantly, the self-stimulation reaction of the lateral hypothalamus is a reliable method for studying the reinforcing systems of the brain and reflects the psychic component of addiction to an extent. This is indicated by a gradual increase in the addictiveness coefficient with increasing doses of the psychoactive substances under study. Previously, we and other specialists considered the effect of psychotropic drugs on self-stimulation of the lateral hypothalamus as regards primary reinforcing (unconditional reflexes). This referred to the ability of brain tissue to respond specifically to electrical stimulation by motor response and reduction of the stimulus threshold at repeated stimulation [4, 6, 8]. However, the gradational increasing response to increasing doses of a narcotic, especially when administering psychostimulants such as phenamine, may indicate that self-stimulation and addictiveness coefficient are associated with psychic dependence. This is, in narcology, "the desire to reuse a substance to achieve a specific euphoria" [18].

Three psychoactive substances with varying addictive potential were included in the study: ethanol (0.5–4 g/kg), morphine (1–8 mg/kg), and phenamine (0.5–4 mg/kg). The initial doses were selected as threshold doses for effects on self-stimulation of the lateral hypothalamus. However, it is critical to first consider the data obtained when 0.9% sodium chloride solution (isotonic sodium chloride solution) was administered on self-stimulation. In half of all control groups, repeated administration of isotonic sodium chloride solution resulted in an increase in self-stimulation, whereas in the other half, it resulted in a decrease. In Tables 1–3, the corresponding data are presented as control groups: control group I (increase in self-stimulation) and control group II (decrease in self-stimulation). In all cases, the deviation from baseline with repeated self-stimulation did not exceed 11%, enabling the calculation of the mismatch coefficient, which did not change, decrease, nor increase. Consequently, the mismatch coefficient should not be the sole criterion for evaluating the impact of psychotropic substances. However, its initial value should be considered, as it determines the calculation of the addictiveness coefficient. Based on the experimental data, if the upper limit of the addictiveness coefficient is <1.25 or within a narrow range of this value, then the increase in the addictiveness coefficient due to the influence of a psychoactive drug can be interpreted as psychic dependence. It is crucial to compare with that under the administration of isotonic sodium chloride solution (control), because the initial values of the mismatch coefficient fluctuate significantly (from 0.70 to 1.24 in our experiments). The present study indicates that the addictiveness coefficient was the most informative and unidirectional among the three behavioral indices (pedal push increment, mismatch coefficient, and addictiveness coefficient).

Another distinction of addictiveness coefficient is its progressive increase with increasing dose of the psychoactive substance. This can be observed, for instance, in the case of the psychostimulant phenamine (Table 1). Additionally, addictiveness coefficient demonstrates an increase in comparison with the control values. Thus, the final calculated addictiveness coefficient depends on the initial control values, which can decrease, remain unchanged, or increase with repeated self-stimulation to the administration of isotonic sodium chloride solution (active control). Regarding ethanol control, data were obtained at both high (+9%) and low (–11%) levels of baseline self-stimulation. The mismatch coefficient in this case exhibited either a decrease (control group I) or an increase (control group II). The value was 0.92 in the first case and 1.28 in the second, presenting the only positive value of all the data obtained for this index. Consequently, the addictiveness

coefficient in the active control group was 0.70, showing a deep negative value. These findings indicate that the reinforcing effects of ethanol (0.5–1–2–4 g/kg) result in an approximately 2.4-fold increase in the addictiveness coefficient at doses of 0.5 and 1 g/kg, with a lesser extent of increase at doses of 2 and 4 g/kg. However, all values of the addictiveness coefficient were found to be significantly higher than the control values (Table 3).

Remarkably, ethanol at 2 and 4 g/kg correspond to the state of pronounced and deep intoxication, during which the animal's motor skills are significantly impaired. Furthermore, it is unreasonable to anticipate a notable increase in the addictiveness coefficient at these doses. This conclusion is supported by a comparison of the addictiveness coefficient at the dose of 4 g/kg ethanol (1.16 ± 0.03) with the corresponding indicators of control group I (1.18 ± 0.04), which revealed no significant differences between the two groups.

A comparable phenomenon was observed in evaluating the reinforcing properties of morphine. The maximum degree of increase in the addictiveness coefficient at the dose of 2 mg/kg can be estimated as +61%, the dose of 8 mg/kg as +32%, and doses of 1 and 4 mg/kg as only +13%–14% in comparison with control group II. These data should be evaluated in the context of the control values for the addictiveness coefficient, which in this group (II) amounted to 1.24 ± 0.05, representing a nearly twofold increase compared to that in the ethanol control group. Therefore, it could not be concluded from the obtained data that the addictive potential of morphine in doses of 1–2–4–8 mg/kg is less than that of ethanol (0.5–1–2–4 g/kg) when addictiveness coefficients amounted to +68%–142% of control values (control group II), because in the case of comparison with control group I, addictiveness coefficients amounted only to +23%–42%. Hence, the addictiveness coefficient more accurately reflects the effects of ethanol and morphine on the brain reinforcement systems.

Consequently, the addictiveness quotient is a reliable, straightforward, and convenient quantitative method for assessing the addictive potential of psychoactive compounds. It is suitable for assessing the addictive potential of psychostimulants, but not exclusively. The coefficient is more appropriately compared within a group of similar psychoactive compounds than between different groups. For example, it would be more appropriate to compare morphine, fentanyl, and trimeperidine with each other than to compare morphine to amphetamine, fentanyl to cocaine, or trimeperidine to phencyclidine. If comparisons are to be made between different groups of psychoactive substances, appropriate reference values on which to base such studies should be used. Based on our data, the control values for the addictiveness coefficient should be 1.00–1.25. A decrease in the value of the addictiveness coefficient would indicate greater reinforcing properties of the psychoactive substance, as we observed with ethanol compared to control group II (Table 3). Thus, the controls should be strengthened by increasing the number of observations. Such an approach is beneficial for assessing the narcogenicity of different psychoactive substances.

CONCLUSIONS

The data presented demonstrate the feasibility of calculating the addictive coefficient of a psychoactive substance as the ratio of the proportion of changes in pedal presses to the value of the mismatch coefficient when using the lateral hypothalamic self-stimulation method. For several psychoactive groups of substances, such as psychostimulants, this index shows a clear and directly proportional dose dependence, probably because it is attributed to psychic dependence. However, this pattern is not always observed. In groups in which self-stimulation is not reproduced at a high level (analgesics from the opium group, sleeping pills from the group of barbituric and isobarbituric acid derivatives, and tranquilizers from the benzodiazepine group), the addiction coefficient is not relatively indicative, because these drugs are characterized more by physical dependence. The addictiveness coefficient, along with other quantitative indicators (number of pedal presses and mismatch coefficient), can reflect the actual narcogenic potential of a psychoactive substance. Crucial for the calculation of this indicator are the corresponding reference values, which, according to our data, should be 1.00–1.25. Additionally, when using the method of self-stimulation of the lateral hypothalamus, it is better to use the addiction coefficient for comparison primarily within a group of similar psychoactive compounds, for example, among opiates, barbiturates, benzodiazepines, and psychostimulants, rather than between different groups of compounds.

ADDITIONAL INFORMATION

Authors contribution. All authors made significant contributions to the conception and preparation of the article, and read and approved the final version before publication. P.D. Shabanov, Ya.B. Likhtman, A.A. Lebedev — data analysis, article writing; P.D. Shabanov — development of the general concept.

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AUTHORS INFO

***Petr D. Shabanov,** Dr. Sci. (Medicine, Pharmacology), Professor;
address: 12 Acad. Pavlov st., Saint Petersburg, 197022, Russia;
ORCID: 0000-0003-1464-1127; eLibrary SPIN: 8974-7477;
e-mail: pdshabanov@mail.ru

Yan B. Likhtman,
e-mail: yanlikhtman@mail.ru

Andrei A. Lebedev, Dr. Sci. (Biology, Pharmacology), Professor;
ORCID: 0000-0003-0297-0425; eLibrary SPIN: 4998-5204;
e-mail: aalebedev-iem@rambler.ru

ОБ АВТОРАХ

***Петр Дмитриевич Шабанов,** д-р мед. наук, профессор;
адрес: Санкт-Петербург, Россия, 197022, ул. Академика Павлова, 12; ORCID: 0000-0003-1464-1127; eLibrary SPIN: 8974-7477;
e-mail: pdshabanov@mail.ru

Ян Борисович Лихтман,
e-mail: yanlikhtman@mail.ru

Андрей Андреевич Лебедев, д-р биол. наук, профессор;
ORCID: 0000-0003-0297-0425; eLibrary SPIN: 4998-5204;
e-mail: aalebedev-iem@rambler.ru

* Corresponding author / Автор, ответственный за переписку