ISSN 0022-0930, Journal of Evolutionary Biochemistry and Physiology, 2023, Vol. 59, No. 1, pp. 274–284. © Pleiades Publishing, Ltd., 2023.
Russian Text © The Author(s), 2023, published in Rossiiskii Fiziologicheskii Zhurnal imeni I.M. Sechenova, 2023, Vol. 109, No. 2, pp. 214–228.

EXPERIMENTAL PAPERS

Color Coding Assessment of Haloperidol Effects on Animal Behavior in the Open Field Test

M. S. Makarov[a], Yu. I. Sysoev[b,c,d,e,*], M. K. Guzenko[a], V. A. Prikhodko[b,e], E. Korkotian[a,f,], and S. V. Okovityi[b,e]**

[a] *Perm State National Research University, Perm, Russia*

[b] *St. Petersburg State Chemical and Pharmaceutical University, St. Petersburg, Russia*

[c] *Pavlov Institute of Physiology, Russian Academy of Sciences, St. Petersburg, Russia*

[d] *Institute of Translational Biomedicine, St. Petersburg State University, St. Petersburg, Russia*

[e] *Bechtereva Institute of the Human Brain, St. Petersburg, Russia*

[f] *Weizmann Institute of Science, Rehovot, Israel*
**e-mail: susoyev92@mail.ru*
***e-mail: eduard.korkotian@weizmann.ac.il*

Received September 17, 2022; revised December 18, 2022; accepted January 9, 2023

Abstract—Development of novel approaches to behavioral test data analysis is of considerable importance for both fundamental research and experimental neuropharmacology. Antipsychotic agents used to treat positive and negative symptoms in schizophrenia are of particular interest. Although antipsychotics exert potent effects on animal behavior in simple behavioral tests, they can be difficult to distinguish from other CNS-depressing agents, such as sedatives. In this paper, we propose color coding of video sequences as a method for the analysis of behavioral pattern structure in rats, using the effects of haloperidol, a typical antipsychotic, in the Open field test as an example. The study was carried out on outbred albino male rats weighing 250–300 g. Three-min video sequences of rat behavior in the Open field test were processed using Python and the OpenCV library in the Google Colab 3 environment. Color coding allowed the present ($t = 0$), near-future ($t = 0.33$ s), and the more distant-future ($t = 1.66$ s) location of an animal in the Open field arena to be marked with different colors and overlaid within a single frame. Using the proposed 3-timepoint color coding method, we were able to detect specific effects of haloperidol on animal behavioral patterns, which are undetectable via conventional techniques of behavioral data analysis in the Open field test. This method proved effective for data analysis and processing, and the results were in accordance with other author's data obtained using computerized and conventional visualization techniques.

DOI: 10.1134/S0022093023010222

Keywords: color coding, behavioral testing, Open field, haloperidol, antipsychotics

INTRODUCTION

Schizophrenia is one of the widespread and still understudied mental disorders that affects about 1% of the human population [1]. Although its developmental mechanisms are not fully understood, a number of pharmacological targets have been proposed, acting on which antipsychotics can relieve the symptoms of this disease [2]. Nevertheless, the drugs in current use do not completely come up expectations of physicians and patients, as they do not adequately treat the so-called "minus" symptoms and cognitive impairments. Moreover, the intake of typical antipsychotics inevitably entails the development of such unwanted sequelae as parkinsonism and dystonia in patients [3]. That is why searching for novel drugs to treat schizophrenia is of great importance.

The accomplishment of this task requires efficient methods for screening new potentially active compounds. Among these methods, behavioral tests using small laboratory animals play an important role, because, on the one hand, they model certain aspects of the real clinical situation while, on the other hand, allowing the assessment of the results of in silico and in vitro studies not always extrapolatable to in vivo systems. In addition, behavioral testing is inexpensive, while enabling an answer to the question of whether the compound under study is psychoactive [4].

Detecting exactly the antipsychotic activity of a potential molecule is not a routine task. For example, while the effects of anxiolytics or sedatives can be detected in the Open Field (OF) or Elevated Plus Maze (EPM) tests without any preparation of test animals, in the case of a potential neuroleptic, a prior modeling of schizophrenia is indispensable. To date, many models of this disease have been proposed, which can be divided into pharmacological, surgical and genetic models [5]. Each of these models is quite good at reflecting some or other symptoms of schizophrenia in humans, however, they all take a lot of time and, most importantly, require a huge consumption of laboratory animals.

A fair question arises of whether it is possible to detect the specific antipsychotic effect of a drug using simple behavioral setups without prior modeling of the disease. To do this, it is necessary to search for novel approaches to analyzing video records of animal behavior. Importantly, one of the main difficulties in interpreting the results of behavioral tests is still the subjectivity of assessing some or other criteria by different experimenters, as well as the oversimplification and unidirectionality of the chosen methods of analysis [6].

In the present study, we used the method for detecting dynamic behavioral patterns using color coding of video sequences to analyze the effect of haloperidol on the behavior of laboratory rats in the OF test. Haloperidol was chosen as a reference typical antipsychotic with a strong antipsychotic action without a pronounced sedative effect [7, 8]. The OF test was chosen as the simplest and most frequently used setup in assessing the behavior of small laboratory animals [9].

MATERIALS AND METHODS

The experiments were carried out on 20 male outbred albino male rats weighing 250–300 g. The animals were kept under standard conditions at a 12-h light/dark cycle and ad libitum access to water and food.

The rats were divided into two groups (experimental and control) by 10 animals in each. Experimental animals (haloperidol group) were intraperitoneally (i.p.) administered with a haloperidol solution (Welfarm, Russia) at a dose of 0.3 mg/kg in a volume of 0.5 mL. The animals administered i.p. with physiological solution in the same volume made up a control group. Drug exposure time was 20 min [10], after which the rat was placed in the OF test apparatus (Open Science, Russia) which represented a circular black arena 97 cm in diameter, divided into 19 segments of equal area and having holes in the floor. Video sequences were recorded for 3 min using a Canon 5D camera (Canon Inc., Japan) at the rate of 30 frames per second and illuminance level of 250 lux (with uniform illumination of the whole arena and no illumination gradient). The room place with the OF test apparatus was screened from the rest of the working space using a monochrome medical privacy screen. The camera operation was controlled remotely using the EOS Utility software (Canon Inc., Japan); images were displayed on the experimenter's monitor.

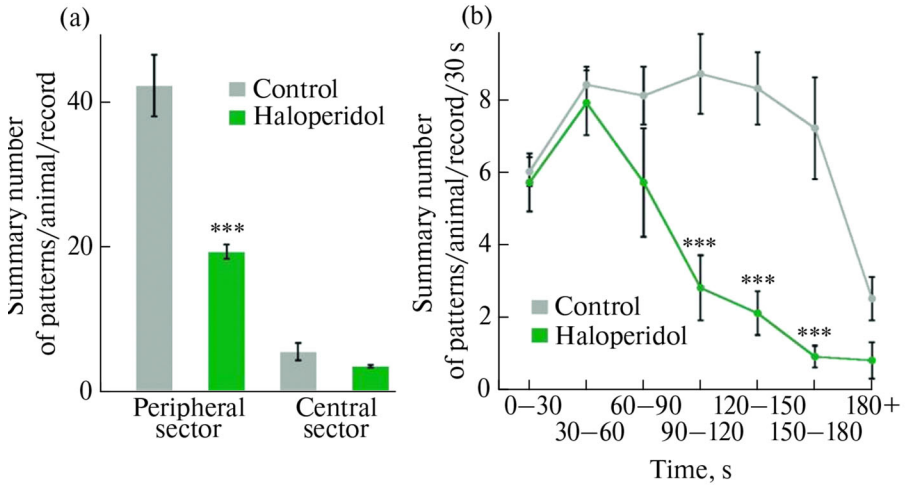

Fig. 1. General locomotor activity in the control and haloperidol rat groups. (a) Mean total number of motor patterns in the peripheral and central Open field segments over the entire recording time (3 min). (b) Locomotion dynamics in the Open field test during consecutive 30-s time intervals. *** $p < 0.001$.

The following behavioral motor patterns were recorded during video analysis: left/right head/body turns, forward movement, 180° turns (turn back movement), wall-supported and unsupported rearing on hind legs, hole exploration (head dipping/peeping into holes), sniffing the air, grooming, and freezing. Pattern count-based validation of general locomotor activity was accomplished by a standard method of manual counting of sector boundary crossings. Part of the video records were viewed in their initial form, with the main motor patterns being identified and recorded. Next, using Python and the OpenCV library in the Google Colab 3 environment, the records were processed. Using color coding, the present ($t = 0$), near future ($t = 0.33$ s), and more distant-future ($t = 1.66$ s) positions of the animal were marked with different colors and overlaid within the same frame.

The data were statistically processed using Student's *t*-test or Mann–Whitney *U*-test using PAST 4.03 and Excel 2016 (Microsoft, USA). Normality of data distribution in the samples was assessed using the Shapiro–Wilk test. Two-way repeated measures analysis of variance (ANOVA) followed by the Tukey's pairwise comparison post hoc test were used to analyze the dependence of motor activity on the time factor. Intergroup differences were considered statistically significant at $p < 0.05$. Data in bar charts are presented as $M \pm SEM$.

RESULTS AND DISCUSSION

The OF test allows assessing locomotor activity, orientational-exploratory behavior, and anxiety level in rats and mice [11]. Since an analysis of behavioral motor patterns is the basis for the OF test, it is the motor patterns that were analyzed first out of the whole complex of the patterns identified.

Among the variety of motor patterns for assessing general locomotor activity in the center and at the periphery of the arena, the following were taken into consideration: 180°, right and left turns, forward movement, as well as right, left and forward head reorientation. Statistically significant differences in the locomotor activity of control and haloperidol-treated animals were only obtained at the periphery of the arena. In the haloperidol group, locomotor activity was significantly lower: the total number of patterns over the entire recording period was 19.3 ± 1.2 vs. 42.2 ± 4.2 in the control group ($p < 0.001$) (Fig. 1a).

The standard method for assessing locomotor activity by counting sector boundary crossings revealed the same regularity: 92.3 ± 10.5 and 32.9 ± 4.9 sector crossings in the control and haloperidol groups, respectively ($p < 0.001$). The difference in the number of sector crossings in the same group is due to the counting approach: when counting the chosen patterns, the sector-crossing

event was only recorded upon action initiation, after which the animal was free to carry on moving and crossing several sectors. In the long run, both methods can be used to reveal abnormalities in the structures responsible for movement initiation and planning. At the same time, by far lower locomotor activity was clearly observed in the central segments of the arena; no statistically significant intergroup differences were found in the center of the OF (Fig. 1a).

Figure 1b shows the mean sums of patterns within each successive 30 s of the experiment. Thus, the total recording time was reduced to 7 temporal zones. The dynamics of ups and downs of motor activity were traced, however, during the first minute of the experiment, the activities in both groups were statistically indistinguishable. Starting from the second minute, haloperidol-treated animals showed a marked decrease in their activity. In the control group, a similar decrease also took place, although it was only observed during the last minute of the recording, when the mean numbers of patterns in the rats of both groups came closer again.

Such a downward tendency of locomotor activity may have been a consequence of hypokinesia induced by dopaminergic deficiency that developed against haloperidol administration and indirectly affected locomotion. The neurotransmitter dopamine plays an important role in the modulation of motor functions [13], while dopamine deficiency or blockade of dopamine receptors lead to the development of a number of pathological behaviors, including those related with locomotor activity [14].

Two-way repeated measures ANOVA revealed a significant intergroup difference that was amplified by the time factor ($p < 0.001$), while the Tukey's pairwise comparison post hoc test showed that the locomotor activity dynamics in the groups was significantly different within the following periods: 90–120, 120–150, and 150–180 s ($p < 0.001$). In other words, the haloperidol-treated animals stopped moving around the OF much earlier than the control individuals.

It has previously been found that haloperidol, like many other typical antipsychotics, exerts a considerable side effect on locomotor activity and causes pronounced extrapyramidal disorders, which are clinically manifested by tremor, bradykinesia, muscle rigidity, etc. [15]. This circumstance could not help affecting the pattern of rat activity. The frequency and duration of freezing episodes in the control and haloperidol groups were significantly different (Figs. 2a and 2b). Overall, the movements against the haloperidol background were somewhat slower and were accompanied, as mentioned above, by head turns (Fig. 2c). Intermittent speeding-up and slowing-down episodes were often observed in the control group as well, because they are the elements of normal locomotion in rats [16–18]. However, it is important to note that such acceleration–deceleration alternations were observed far less frequently in the haloperidol group compared to the control, suggesting the appearance of pronounced drug-induced locomotor stereotypy and monotony (Fig. 2d). Behavioral monotony, and perhaps a related decrease in exploratory activity, were manifested by fewer supported rears (Fig. 2e) (4.5 ± 1.0 vs. 1.3 ± 0.4 in control vs. haloperidol groups, respectively; $p < 0.01$), as well as by a decrease in the number of exploratory hole-sniffing episodes (6.9 ± 1.9 vs. 2.0 ± 0.8 in control vs. haloperidol groups, respectively; $p < 0.05$).

At the same time, no intergroup differences were revealed for the other conventional behavioral patterns, such as rearing without support, sniffing the air as one of the manifestations of the orientational reflex, and grooming.

The application of the method of temporal-color coding, which allows overlaying three consecutive animal's positions within a single frame—in the present, near future (in 0.33 s), and more distant future (in 1.66 s), enabled us to record one or another behavioral event most objectively (as far as it is possible in principle). The behavioral patterns identified using this method are exemplified in Fig. 3.

Figure 3a shows a typical example of brief sniffing of the air (yellow, arrow), which is quickly replaced by another behavior (red). Sniffing at the arena walls ((3b), yellow, arrow) looks similar, with the difference that it continues to occur in the more distant future with an offset (red). A typical example of grooming is shown in panel (c), while hole exploration in panel (d). Panels (e) and (f) demonstrate brief unsupported and supported

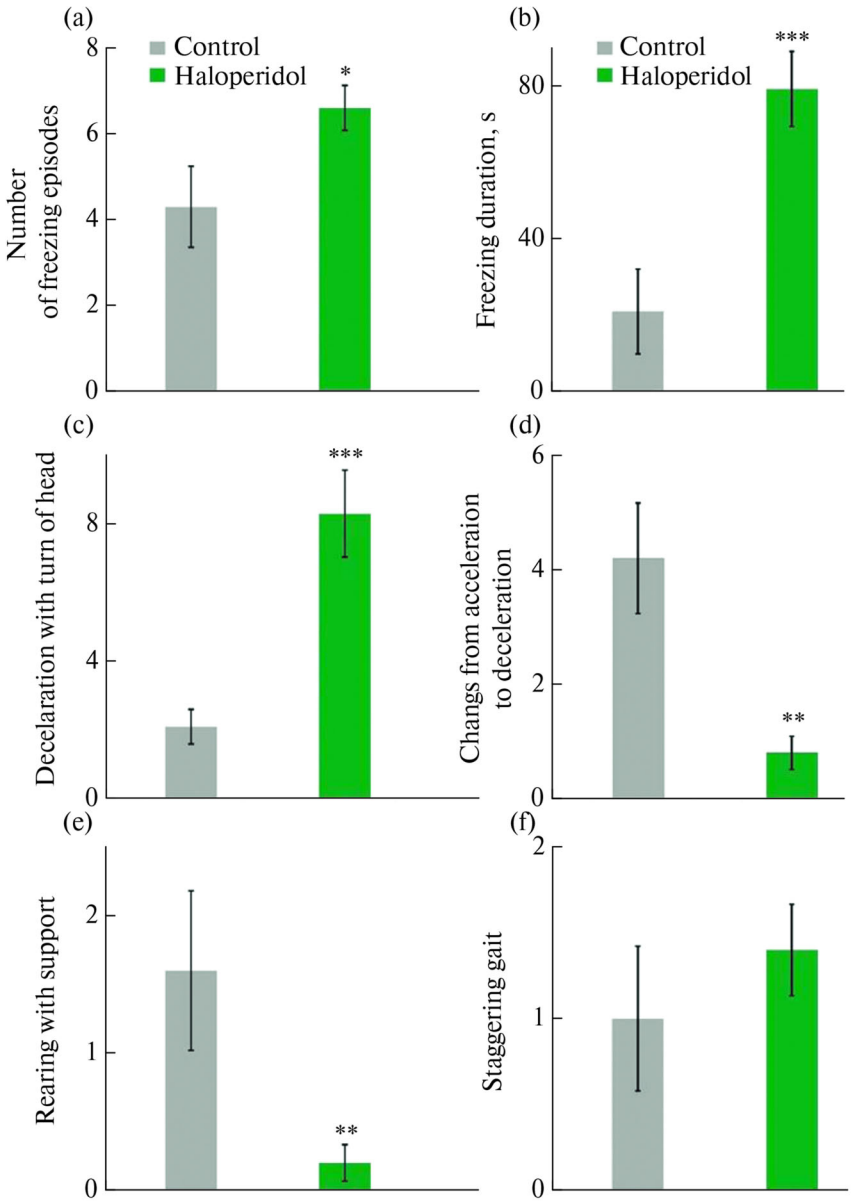

Fig. 2. Frequency of some behavioral motor patterns in the Open field test, as observed in the control and haloperidol rat groups. (a) Mean number of freezing episodes. (b) Total duration of freezing episodes. (c) Number of slowing-down episodes with simultaneous head turns or "nods". (d) Number of speeding-up and slowing-down alternations. (e) Mean number of supported rearing episodes. (f) Cases of staggering, shaky gait. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$.

rears (gray only, arrows) replaced in both cases in the near future by other types of behavior (red).

The above patterns of behavioral activity typically indicate the degree of animals' orientational–exploratory activity and anxiety, as well as the emotional component as such. For example, a study by Zvezdochkina et al. [14] revealed a pronounced decrease in rat orientational–exploratory behavior in the OF test after haloperidol administration, and a decrease in the grooming pattern frequency, which suggested an increase in animal anxiety and the development of inhibitory processes in the CNS.

However, such a pattern as grooming cannot be identified as an unambiguous anxiety marker, as it can also imply a comfortable and quiet state in which the animal is staying. Proceeding from, the variability of such a pattern should not be

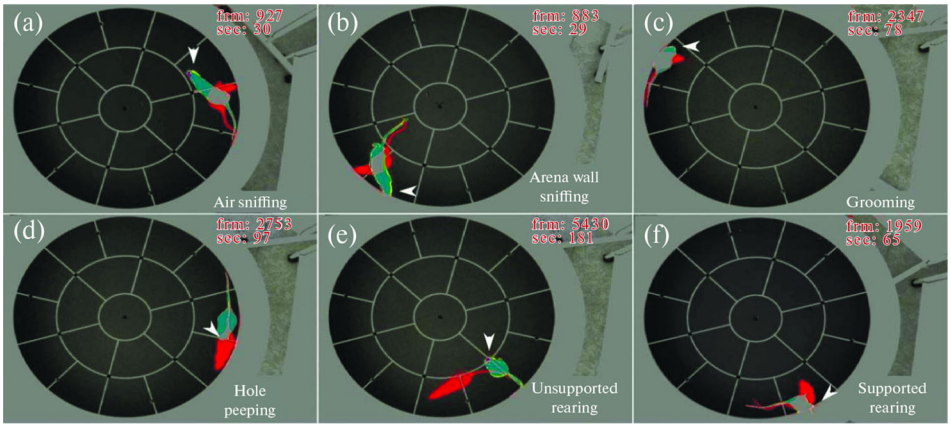

Fig. 3. Representative examples of some behavioral patterns, color-coded in the present, near future (in 0.33 s; gray and yellow), and more distant future (in 1.66 s; red). (a) Sniffing of the air above the arena. (b) Sniffing at the arena walls. (c) Grooming. (d) Sniffing of holes in the arena floor. (e) Wall-unsupported rearing. (f) Wall-supported rearing. Arrows indicate the regions critical for pattern identification.

regarded as a marker of the effect of haloperidol or any other psychoactive compound. Moreover, one cannot deny that the emotional component plays an important role in motor functions, since it has been found out that it is the mesocorticolimbic pathway that modulates the reactions that are associated with fear and anxiety [19].

Unfortunately, the allowance for such behavioral patterns is complicated and carries the risk of excessive subjectivity of assessments. The analysis of simple motor patterns, whose interpretation is unambiguous, appears much more effective and reasonable. These simple motor parameters include forward movement, 180є turn, left and right turns, and head turns. Figures 4a–4f show a pairwise comparison of these motor patterns in two rat groups. Statistical analysis revealed that the differences were statistically significant for all patterns except head turns.

In the control group, the mean number of forward movements was 12.2 ± 2.4 vs. 3.6 ± 1.0 in the haloperidol group ($p < 0.01$) (Fig. 3a), 180° turns—3.3 ± 0.4 vs. 1.8 ± 0. 5 in the haloperidol group ($p < 0.05$) (Fig. 3b), right or left turns—11.8 ± 1.9 and 11.6 ± 2.2 vs. 3.2 ± 0.6 and 3.6 ± 0.6 in the haloperidol group, respectively ($p < 0.001$ and $p < 0.01$, respectively) (Figs. 3c, 3d). Taken together, these data clearly indicate a reduced baseline locomotor activity, which includes forward movement and turns, while the other motor events (head turns), orientational reflexes, and general anxiety level remain approximately intact.

However, the question remains unclear to what extent the current position of the animal, or its slight offset for 0.3 s, can serve as a predictor of further movement. In other words, is there a relationship between the vector of short-term offset and that of more distant movement? If such a relationship does exist among the intact animals, then to what extent does it persist or violate under the effect of haloperidol?

Thus, due to a 3-timepoint color coding, we attempted to predict the future location of animals by certain regularities. To do this, we selected 4 patterns in the more-distant future: forward movement, 180° turn; right or left turns. According to this set, the collected data were divided into the four appropriate groups.

Next, we hypothesized that animal's head, tail, or body turns to one or another side serve as signs that can be used to determine the likelihood for certain patterns to arise in the more distant future ($t = 1.66$ s). It was also noted that animals often turned their tail and/or head toward future movement. Therefore, these three factors were chosen for analysis at the present time and in the near future. Each of the factors corresponded to the future behavior in the following way: whether animal's head, tail or body were facing the same direction where the animal was going to move in 1.66 s, namely, forward, backward (turn back),

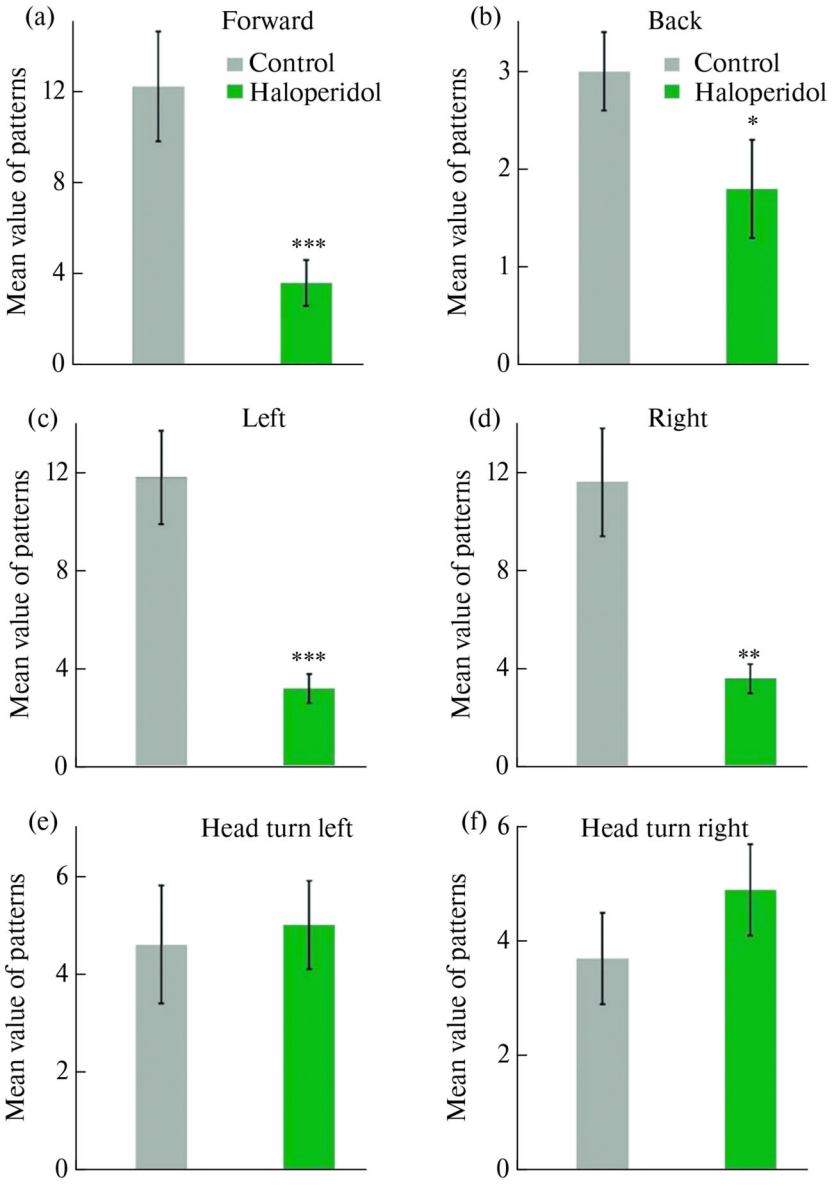

Fig. 4. Mean number of simple motor events recorded in the control and haloperidol rat groups. (a) Forward—forward movement. (b) Turn back—movement with 180° turn. (c) Left—left body turn. (d) Right—right body turn. (e) Left head turn. (f) Right head turn. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$.

right or left. Figure 5 exemplifies how the sorting was carried out in accordance with these factors.

In Fig. 5, panel (a) shows the offset (in yellow) of the head, tail and whole body, roughly codirectional with the future animal's position (red). Panel (b) demonstrates a very slight non-co-directional offset of the head and tail (yellow) relative to the near-future position (red). Panel (c) depicts a pronounced codirectionality, while panel (d) shows a weak counterdirectionality (non-co-directionality).

The animal's head, tail and body most often assumed an independent position, so they were considered separately in further analysis. When analyzing the obtained data on the position of the head, tail and body as predictive criteria for future movement, there were revealed different tendencies that varied considerably from one animal to another, as well as between the main types of locomotion (forward, turn back, left and right turns). However, did these tendencies depend on the effect of haloperidol? To answer this question,

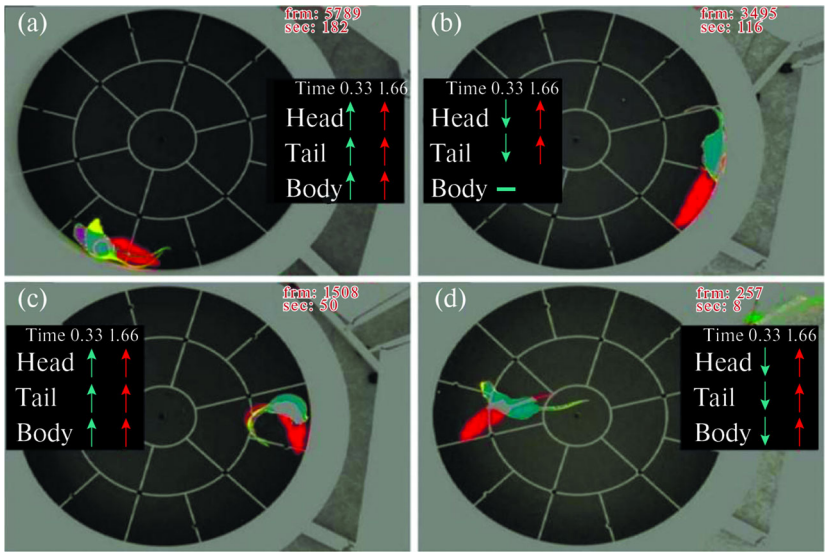

Fig. 5. Examples of co- and non-co-directional offset of the rat head, tail and body in the present and in 0.33 s (gray and yellow) relative to their location in 1.66 s (red). (a) An example of a 180° turn. (b) An example of forward movement. (c, d) Examples of right and left turns.

it was necessary to calculate the codirectionality to non-co-directionality ratio in each animal in each of the motor patterns. Since there was no solid evidence to consider left and right turns separately, they were combined into a common pattern. In the analysis of rectilinear motion, the animal's head, tail and body occupied co- and non-co-directional positions in approximately the same number of cases. However, in other cases, these body parts more often occupied rather a non-co- than a codirectional position. In this regard, the non-co-directionality to codirectionality proportion was applied, but not vice versa, although it was not of fundamental importance. A sort of "directionality index" was thus calculated, representing the proportion of the total number of non-co-directional to codirectional head, tail and body positions for each of the three motor patterns (forward movement, turn back, right and left turns. All proportions were calculated individually for each animal and then summarized in Tables 1–3.

The calculation algorithm for the directionality index was as follows.

1. The patterns of forward movements, turn back (180° turns), right or left turns were selected.

2. For each animal in each pattern, the position of the head, body and tail both at the present and near-future (0.33 s), as well as more-distant-future (i.e., in 1.66 s), time were considered. If the position of any body part at the present and near-future time coincided with the position of the same body part in the more-distant future, this movement was called codirectional; otherwise, it was considered non-co-directional. For example, in Fig. 5b, one can see that the head, body and tail are turned to the right, hence we added by one codirectional motion for each body part for this animal.

3. Finally, in each animal and pattern for each body part, the number of co- and non-co-directional movements was summed up, and the ratio of non-co- to codirectional movements was then calculated.

In this form, the data assumed the appearance suitable for a two-way ANOVA. The first factor reflected the directionality indices for the head, tail and body, distributed between rows 1 to 10 (for the head), 11 to 20 (for the tail), and 21 to 30 (for the body). The second factor matched the groups (control or haloperidol) situated in two columns. The results of two-way ANOVA carried out in the MATLAB R2020a environment are presented in Tables 1–3.

From Table 1, it follows that while moving forward, the directionality index significantly depended on the animals' body parts which behaved differently. At the same time, haloperidol administration had no statistically significant

Table 1. Two-way analysis of variance for forward movement (control/haloperidol)

Forward movement	Sum-of-squares (SS)	Degrees of freedom (df)	Mean squares (MS)	F	Probability; Prob > F
Columns (animal groups)	0.0001	1	0.00009	0	0.99
Rows (body parts)	27.85	9	3.1	2.97	0.01
Interaction	7.8	9	0.9	0.8	0.6
Error	41.7	40	1.04		
Total	77.4	59			

Table 2. Two-way analysis of variance for turns back (control/haloperidol)

Forward movement	Sum-of-squares (SS)	Degrees of freedom (df)	Mean squares (MS)	F	Probability; Prob > F
Columns (animal groups)	10.5	1	10.5	10.7	0.002
Rows (body parts)	16.1	9	1.8	1.9	0.1
Interaction	15.4	9	1.7	1.7	0.1
Error	39.5	40	0.99		
Total	81.6	59			

Table 3. Two-way analysis of variance for right and left turns (control/haloperidol)

Forward movement	Sum-of-squares (SS)	Degrees of freedom (df)	Mean squares (MS)	F	Probability; Prob > F
Columns (animal groups)	47.85	1	47.85	30.05	0.0000005
Rows (body parts)	126.7	19	6.7	4.19	0.000003
Interaction	100.3	19	5.3	3.32	0.0001
Error	127.4	80	1.6		
Total	402.2	119			

effect on the non-co-directionality to codirectionality proportion (Fig. 6) and, accordingly, there was no interaction between the factors.

From Table 2, it follows that the factor of the animal group (control or haloperidol) had a statistically significant effect ($p < 0.01$) on the directionality index. At the same time, the factor of the influence of head, tail or body position, as well as their interaction with the animal group, was not detected. Consequently, the hypothesis about the effect of haloperidol on future locomotion pattern planning is confirmed: after haloperidol administration, non-co-directionality relative to future movement stops dominating over codirectionality, as observed in the control (Fig. 6).

Lastly, Table 3, which combines the information on left and right turns, demonstrates a very high level of statistical significance that the directionality index depends on the animals' affiliation with one of the groups. Nevertheless, the effect is also associated with the position of a specific body part (head, tail or body). Moreover, there is a statistically significant interaction between these factors, and, thus, the haloperidol effect is reflected to the greatest extent in the position of the head and body, and to a lesser extent, in the position of the tail. Anyway, as with the turn back movement, haloperidol administration sharply reduces the

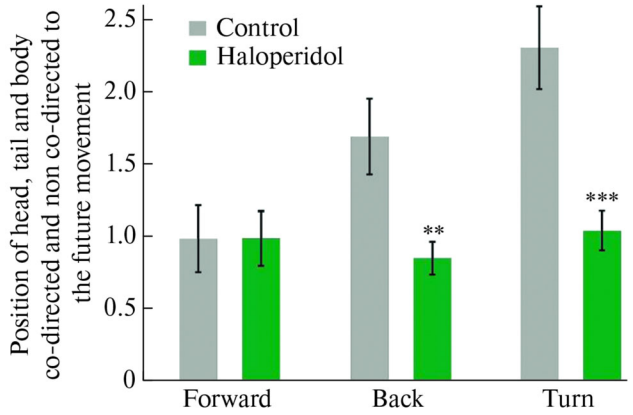

Fig. 6. Directionality indices for the rat head, tail and body in the Open Field test before one of the simple motor patterns: forward movements, turn back (with a 180° turn), left or right turns. The directionality index was calculated individually for each animal and for each motor pattern by dividing the number of non-co-directional head, tail or body locations by the number of codirectional locations. Differences between control and haloperidol groups were statistically significant for 180° and left/right (side) turns, but not for forward movement (see Tables 1–3), *** $p < 0.001$, ** $p < 0.01$.

frequency of the non-co-directional body part position before the turns (Fig. 6).

We can, therefore, affirm that haloperidol is to a much greater extent (vs. controls) associated with a codirectional body orientation when turning sideways and 180°, whereas moving forward, it has no effect at all (Fig. 6). In other words, in certain cases, the animal becomes more predictable, which may be due to haloperidol-induced bradykinesia.

The 3-timepoint color-coding method, we applied here, proved its effectiveness in data analysis and processing. The results obtained are well consistent with the literature data obtained using both conventional and computerized imaging methods. An indisputable advantage of the proposed method is that it opens up new possibilities in working with biological images, employs a relatively simple technology, and expands the analytical arsenal of modern studies by objectifying the process and thus reducing the impact of the human factor. The method allows recording rather small movements and visualization of the dynamics of objects overlaid within the same frame. We believe that this method, when combined with others, will help assess the effects of psychoactive compounds in their pharmacological screening more accurately and quickly.

AUTHORS' CONTRIBUTION

Conceptualization and experimental design (E.K., S.V.O., Yu.I.S.); data collection and processing (M.S.M., M.K.G., V.A.P.); illustrations (M.K.G., E.K.); writing and editing the manuscript (E.K., S.V.O., Yu.I.S., M.S.M., V.A.P.).

FUNDING

The work was implemented using the equipment of the SPCPU Analytical Center within the Agreement no. 075-15-2021-685 of 26.07. 2021, supported by the Ministry of Education and Science of the Russian Federation, and the St. Petersburg State University project no. 73025408.

COMPLIANCE WITH ETHICAL STANDARDS

The study was carried out in accordance with the principles of the Basel Declaration, the Order of the Ministry of Health of the Russian Federation no. 199n "On approval of the rules for good laboratory practice" of 01.04.2016, and the recommendations of the Bioethics Committee of the St. Petersburg State Chemical and Pharmaceutical University (SPCPU) of the Ministry of Health of the Russian Federation.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

1. Harris L, Wayland P, Umrania Y, Krishnamurthy D, Rahmoune H, Bahn S (2013) Schizophrenia: metabolic aspects of aetiology, diagnosis and future treatment strategies. Psychoneuroendocrinology 38(6): 752–766. https://doi.org/10.1016/j.psyneuen.2012.09.009
2. Kalitin KY, Spasov AA, Mukha OU, Pridvorov GV, Lipatov VA (2021) Pharmacological Targets and the Mechanism of Action of Antipsychotic Agents in the Framework of the Neurochemical Theory of the Pathogenesis of Schizophrenia. Russ J Physiol 107(8): 927–954. (In Russ). https://doi.org/10.31857/S0869813921080070
3. Vaiman EE, Shnayder NA, Khasanova AK, Strelnik AI, Gayduk AJ, Al-Zamil M, Sapronova MR, Zhukova NG, Smirnova DA, Nasyrova RF (2022) Pathophysiological Mechanisms of Antipsychotic-Induced Parkinsonism. Biomedicines 10(8): 2010. https://doi.org/10.1007/s40120-018-0105-0
4. Drozdov AL, Demchenko EM, Ejjyad A, Nerush OP (2011) Influence of psychotropic drugs on spontaneous behavioral activity of albino rats. Visn Dnipropetr Univ Ser Biol Med 2(1): 47–53. (In Russ). https://doi.org/10.15421/021108
5. Białoń M, Wąsik A (2022) Advantages and Limitations of Animal Schizophrenia Models. Int J Mol Sci 23(11): 5968. https://doi.org/10.3390/ijms23115968
6. Tecott LH, Nestler EJ (2004) Neurobehavioral assessment in the information age. Nat Neurosci 7(5): 462–466. https://doi.org/10.1038/nn1225
7. Drobizhev MYu, Ovchinnikov AA (2012) Why a contemporary classification of antipsychotics is needed? Rus Med J 20(29): 1449–1457. (In Russ).
8. Irving CB, Adams CE, Lawrie S (2013) Haloperidol versus placebo for schizophrenia. Cochrane Database Syst Rev (11): CD003082. https://doi.org/10.1002/14651858.CD003082.pub3
9. Prut L, Belzung C (2003) The open field as a paradigm to measure the effects of drugs on anxiety-like behaviors: a review. Eur J Pharmacol 463(1–3): 3–33. https://doi.org/10.1016/S0014-2999(03)01272-X
10. Sysoev YI, Shits DD, Puchik MM, Prikhodko VA, Idiyatullin RD, Kotelnikova AA, Okovityi SV (2022) Use of Naïve Bayes Classifier to Assess the Effects of Antipsychotic Agents on Brain Electrical Activity Parameters in Rats. J Evol Biochem Phys 58: 1130–1141. https://doi.org/10.1134/S0022093022040160
11. Carola V, D'Olimpio F, Brunamonti E, Mangia F, Renzi P (2002) Evaluation of the elevated plus-maze and open-field tests for the assessment of anxiety-related behaviour in inbred mice. Behav Brain Res 134(1–2): 49–57. https://doi.org/10.1016/s0166-4328(01)00452-1
12. Wahlsten D (2011) Mouse behavioral testing. How to use mice in behavioral neuroscience. Acad Press, Cambridge (MA).
13. Zhai S, Shen W, Graves SM, Surmeier DJ (2019) Dopaminergic modulation of striatal function and Parkinson's disease. J Neural Transm (Vienna) 126(4): 411–422. https://doi.org/10.1007/s00702-019-01997-y
14. Zvezdochkina NV, Muranova LN, Andrianov VV, Arkhipova SS, Gaĭnutdinov KhL, Golubev AI, Pleshchinskiĭ IN (2004) Locomotor reactions and excitability of neurons during the blockade of dopamine by haloperidol in vertebrate and invertebrate animals. Russ J Physiol 90(11): 1381–1392. (In Russ).
15. Strange PG (2008) Antipsychotic drug action: antagonism, inverse agonism or partial agonism. Trends Pharmacol Sci 29(6): 314–321. https://doi.org/10.1016/j.tips.2008.03.009
16. Alves JA, Boerner BC, Laplagne DA (2016) Flexible Coupling of Respiration and Vocalizations with Locomotion and Head Movements in the Freely Behaving Rat. Neural Plast 2016: 4065073. https://doi.org/10.1155/2016/4065073
17. Bouët V, Borel L, Harlay F, Gahéry Y, Lacour M (2004) Kinematics of treadmill locomotion in rats conceived, born, and reared in a hypergravity field (2 g). Adaptation to 1 g. Behav Brain Res 150(1–2): 207–216. https://doi.org/10.1016/S0166-4328(03)00258-4
18. Shishelova AY, Aliev RR, Raevsky VV (2015) Early sensory experience determines variety of exploratory behavior in adult age. Exp Psychol (Russia) 8(1): 73–84. (In Russ).
19. de Souza Caetano KA, de Oliveira AR, Brandão ML (2013) Dopamine D2 receptors modulate the expression of contextual conditioned fear: role of the ventral tegmental area and the basolateral amygdala. Behav Pharmacol 24(4): 264–274. https://doi.org/10.1097/FBP.0b013e32836356c4

Translated by A. Polyanovsky