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INDUCED DEPRESSION IN A COHORT OF RATS VIA COMMUNICATION

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**ИНДУЦИРОВАННАЯ ДЕПРЕССИЯ В КОГОРТЕ КРЫС ПОСРЕД-
СТВОМ КОММУНИКАЦИИ**

Требуется больше исследований, чтобы в полной мере понять суть феномена инфекционной депрессии. Непонимание этого феномена берет начало в ограниченности данных. В настоящее время нет методов исследования трансмиссивной депрессии. Таким образом, понимание механизмов, вовлеченных в процесс заражения, предотвращения, подавления и лечения, остается загадкой. Наша цель заключалась в том, чтобы создать метод оценки инфекционной депрессии у крыс посредством коммуникации.

Процесс индукции депрессии состоял из некоторых стрессовых мероприятий, описанных в разделе методы и материалы. Крысы выполняли данные виды деятельности в течение пяти недель, после чего их тестировали на наличие депрессии при помощи анализа на аффинность с сахарозой. Крысы, которые продемонстрировали депрессивное поведение, находились в пространстве со здоровыми в течение еще пяти недель в соотношении 1 : 2. Для подтверждения результатов мы провели тест на сахарозу, тест с открытым пространством и тест с принудительным плаванием в конце сожительства.

В нашем эксперименте мы продемонстрировали, как здоровые крысы стали инфицированными, проведя много времени в замкнутом пространстве с депрессивными крысами. Аналогично, инфицированные крысы оказывали заметное положительное воздействие на крыс в состоянии депрессии. Принимая во внимание неполноценный характер теста с принудительным плаванием у крыс с посттравматическим расстройством, более емкие по своему характеру исследования могут понадобиться для дальнейшей валидации этой процедуры.

Ключевые слова: инфекционная депрессия, грызуны, анализ на аффинность с сахарозой, тест с открытым пространством, тест с принудительным плаванием.

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More research is required to grasp the phenomenon that is infectious depression entirely. Misunderstandings of this phenomenon stem from lack limited data. There are presently no methods for investigating transmissible depression. Thus, understanding the mechanisms involved in the processes of contagion, preclusion, repression, and treatment remains a mystery. Our aim here was to construct a method of evaluating infectious depression in rats via communication.

The induction process for depression consisted of some very stressful activities detailed in the method and material section. Rats were allowed to navigate these activities over five weeks, after which they were tested for depression by their affinity to sucrose. Those rats that showed depressive behaviors were allowed to share a space with healthy ones for a further five weeks in a 1 : 2 ratio. For confirmation of results, we run sucrose test, open field test, and forced swim test at the end of cohabitation.

We showed in our experiment how healthy rats became infected after spending a considerable amount of time caged with depressed rats. Likewise, infected rats had a noticeable positive effect on the depressed rats. Given the unusable nature of rats post-trauma after the use of the forced swim test, more in-depth studies may be required for further validation of this procedure.

Key words: Infectious depression, rodents, cohabitation sucrose test, open field test, forced-swim test.

Introduction

Recent publications have proven the ease with which individuals can transfer mental diseases others (Hill et al., 2010). The behavior and degree of interaction of the sick predominantly determine the way in which they spread the illness. It is the rapport between sick and healthy individuals that ultimately defines how people acquire this emotional infection. The time needed for depression to fully kick in depends on the intensity and frequency of the relationship, as well as on the resilience of the healthy individuals (Fowler & Christais, 2008).

Given the gravity of infectious depression, past results have primarily dwelt on the negative side of the equation, revealing the enormity of future impact that extends to the infection of all who are a part of the depressed's life (Joiner, 1994; Siebert, 2004; Joiner, 2006; Bastiampillai et al., 2013). Personal frailties and economic problems are partial reasons for undesirable inclinations to infectious depression studies. An investigation

found fatalities to reach 17.1% in the US (Rosenquist et al., 2011), while other studies have reported the nondiscriminatory nature of the disease that is known to ravage people and places with no consideration of gender, age, and status, often leaving them in poor health (Lenze et al., 2001; Creed et al., 2002; Gaynes et al., 2002; Dunlop et al., 2005; Soboci et al., 2007; Saarni et al., 2007). Disabilities that sometimes involve suicides are also eventualities of depression, with numbers of deaths reported at 850,000 a year (Lang & Borgwardt, 2013). Economically, the ability to work is lost with depression and expenses often skyrocket with treatment (Wang et al., 2006). Not only does the disease deprive patients of the aptitude to work, but it also massively reduces the general workforce because those who care for the sick can also not fulfill their other obligations.

In the fight against depression, only about 60–80% of those to whom antidepressants are available often report getting better, with a majority, especially in less developed areas, not even able to lay their hands on the prescription drugs. Some who receive treatment but do not heal, suffer side effects and some follow instructions poorly, despite the sometimes undesirable outcomes and large expenses (Keller et al., 2002; Pirraglia et al., 2004).

For the first time, we are putting together a guide for evaluating infectious depression and are presenting a double-edged outcome according to our findings, with the aim that further studies shed more light into a grim phase of this ever-dangerous disease. The methods involved in inducing depression are stress-related and may, with time and more discovery, not be ideal for experiments that intend to use the rats for further evaluation. Given that we set out mostly to understand the mechanism with which this disease acts and how to prevent, handle and treat patients more efficiently, we considered the test a success (Boyko et al., 2015).

Materials and Methods

We carried out our tests following the recommended guidelines of the Helsinki and Tokyo declarations and according to those for the ‘Use of Experimental Animals of the European Community.’ The Animal Care Committee of the Ben-Gurion University of the Negev also approved of our investigations.

We used pathology-free Sprague-Dawley rats that weighed in the range 300 to 350 g (Harlan Laboratories, Israel). We housed three rats in each case in a 50–50 day and night cycles, with unlimited chow and water and allowed for adaptation over two weeks. We then tested the rats for any signs of depression with the sucrose preference test. Finding that none of them showed depressive symptoms, we proceeded to separate the rats into three groups: 30 for control, 30 for infection, and 60 for depression.

Inducing depression in rats (Zeldets et al., 2018)

To produce depressive behaviors in the group of 60 rats, we subjected them to any two of some enduring activities over five weeks, one at day and one at night (Willner, 2005). We used the following chronic exercises:

- overstuffing cages with rats (six rats in one cage) for 18 hours;
- angling their cages at 45 min for 3 hours;
- depriving rats of food for 18 hours;
- depriving rats of water for 18 hours and then exposing them to empty bottles for an hour;
- wetting their bedding with 300 ml of water for 8 hours;

- exposing rats to non-stop lighting for 24 hours and then to reversed light and dark cycles for 12 hours, two times a week;
 - placing rats in a hot area (40 °C) for 5 minutes at night.
- Following induction, we confirmed depression by rerunning the sucrose preference test.

Generating infection in healthy rats (Zeldets et al., 2018)

To create a depression in healthy rats, we housed two depressed rats with one healthy rat in each cage for five weeks, forming an experimental cohort of 30 pens. We let the rats have free access to food and water for the entirety of the cohabitation. In the end, we performed sucrose preference, open field, and forced-swim tests to validate our hypothesis.

Testing for preference to sucrose (Boyko et al., 2013a)

We carried this procedure out in the dark cycle. To test for rats' preference to sucrose, we first habituated rats to the taste of glucose individually with 100 ml of 1% sucrose solution administered via a bottle for 24 hours. After the habituation period, we starved the rats of food and water for 12 hours. Next, we gave each rat 100 ml each of sucrose and water via the similar bottles, for 4 hours. At the end of the 4 hours, we recorded the amount of sucrose and water consumed (in ml) and calculated the rats' preference for sucrose using an affinity equation:

$$SP = \frac{\text{amount of sucrose consumed (ml)}}{\text{amount of sucrose consumed (ml)} + \text{amount of water consumed (ml)}}$$

Testing for open field parameters

The open field test is often used in the assessment of the exploratory, locomotive, and nervous instincts of laboratory animals (Boyko et al., 2013b; Slattery & Cryan, 2012). Here, we used it to analyze depression, as has been done before (Kalueff & Tuohimaa, 2004). The principle of this test lies in evaluating two different parameters. Will the rats venture for novelty or will they wilt away in fear of the lights shone in the center of the box? In anxiety, rats prefer staying put, a condition described as thigmotaxis. We used a black lusterless acrylic box, 120 cm by 60 cm by 60 cm, separated into 25% central space and 75% outer space. We ran the test during the dark cycle for 5 minutes, recording the event with a video camera placed 200 cm overhead the box (Boyko et al., 2013b; Slattery & Cryan, 2012). Before putting each animal in the box, we cleaned the case with 5% alcohol. Following the test, we analyzed the distanced covered, center stage velocity, center stage time.

Forced-swim test

We evaluated the ability of rats to persist with escaping confinement in a tight water space or the vulnerability to give up the fight at some stage and only protect themselves from drowning, as stipulated by the principle of the test (Boyko et al., 2013a; Slattery & Cryan, 2012). We examined the animals in the dark phase, first habituating the rats with swimming at room temperature in a glass cylinder 100 cm long, 40 cm wide, and 40 cm deep for 15 minutes. The next day after acclimatization, we recorded 5 minutes videos of the rats swimming in the same conditions as the habituation test and analyzed the foot-ages for stasis, ascension, and defecation.

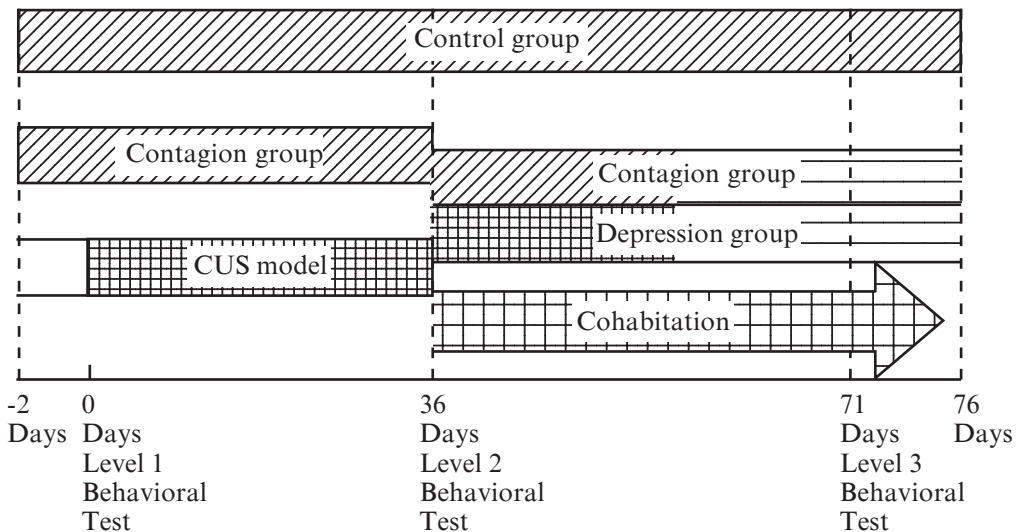


Fig. 1. The experimental scheme (Zeldets et al., 2018). A timeline of the experimental protocol: level 1 — Behavioral Test: Sucrose Preference Test; level 2 — Behavioral Test: Sucrose Preference Test; level 3 — Behavioral Test: Sucrose Preference Test, Open Field Test, Forced Swim Test

Results

Sucrose preference

Results obtained from our experiment confirmed the hypothesis of infectious depression after we found depressive symptoms in healthy rats post-cohabitation with depressed rats. In control rats, the preference for sucrose after five weeks was as high as $(101 \pm 7)\%$ compared to $(65.0 \pm 2.8)\%$, $p < 0.001$ in depressed rats (fig. 2). In 10 weeks, preference for sucrose in control rats was $(95.0 \pm 3.4)\%$ compared to $(72.0 \pm 3.3)\%$, $p < 0.001$ in depressed rats, and $(76.0 \pm 4.7)\%$, $p < 0.001$ in the infected rats after five weeks of living together with depressed rats (fig. 2).

Open field test

Significant differences between values from control experiments and the experimental groups of depression and infectious depression also served to confirm vague premonitions of cohabitation between depressed and healthy individuals. Rats in both experimental groups hardly traveled far from their starting points (depressed rats: $(59.6 \pm 5.7)\%$, $p < 0.01$ and depression infected rats: $(68.1 \pm 6.5)\%$, $p < 0.05$, fig. 3, a) compared to control group rats ($(100 \pm 13)\%$, fig. 3, a). Rats from the experimen-

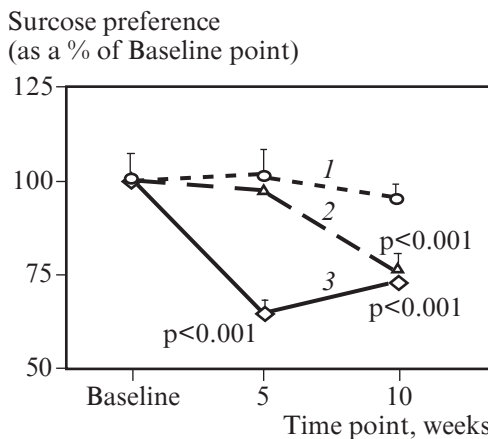


Fig. 2. Test for sucrose preference (Zeldets et al., 2018). We used the one-way ANOVA and the Bonferroni's post hoc test for statistical analysis. Data shown as baseline percentages, conveyed as mean \pm SEM: 1 — control; 2 — depression contagion; 3 — depression

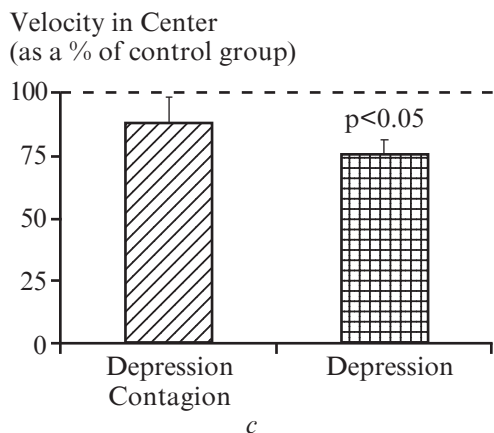
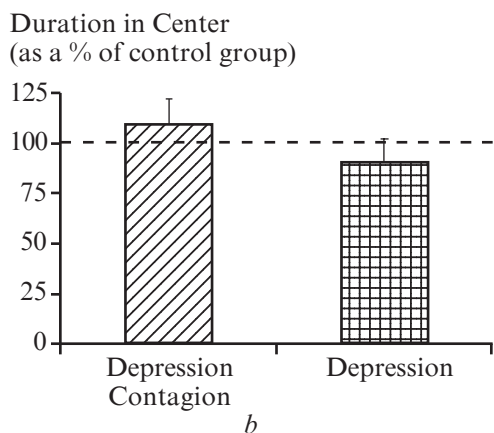
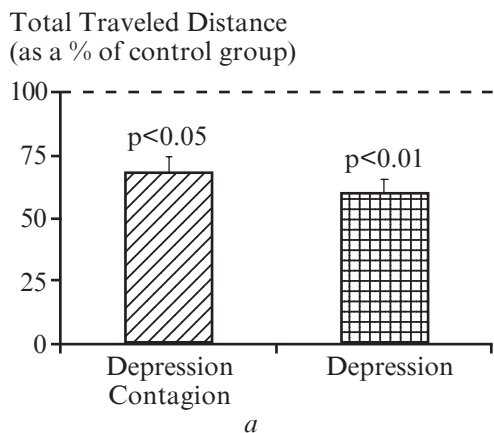


Fig. 3. Test for open field parameters (Zeldets et al., 2018). We used the Kruskal–Wallis and the Mann–Whitney tests in investigating all three settings. Data shown as baseline percentages, conveyed as mean \pm SEM

tal groups also had diminished mean velocities, but only significant in depressed rats (depressed rats: $75.4 \pm 6.0\%$, $p < 0.05$ and depression-infected rats: $88.0 \pm 5.6\%$, $p < 0.005$, fig. 3, c). There was barely any considerable variation in the amount of time spent in the center of the field (fig. 3, b).

Forced-swim test

The inability of the rats in the depression and infectious depression group to keep fighting for escape over an extended period all but confirmed the depressive nature of the rats when compared to control group rats. Both experimental groups of rats showed prolonged immobility after the test, but any significance was registered only in the depression group (depression: $151.0 \pm 3.3\%$, $p < 0.01$ and infectious depression: $107.0 \pm 6.7\%$, fig. 4, a). These two groups showed limited climbing capabilities that massively varied from that of control group rats (depression: $46.0 \pm 5.5\%$, $p < 0.01$, infectious depression: $64.0 \pm 5.4\%$, $p < 0.01$, fig. 4, b). We also collected significant amounts of feces from the experimental groups (depression: $278 \pm 32\%$, $p < 0.01$ and infectious depression: $131 \pm 37\%$, $p < 0.01$, fig. 4, c) compared to less defecation in control rats ($100.0 \pm 22.5\%$, $p < 0.01$, fig. 4, c). With *Post hoc* analysis, we found no remarkable difference between rats in the infectious depression and controls groups. However, the difference between the depression and the control groups was enormous ($p < 0.01$, fig. 4, c).

Discussion

Results obtained from all three of our tests reported the negative impact depressed rats had on healthy rats after five weeks cohabitation. This procedure, as well as confirming our hypothesis, was also the first of its kind established to evaluate depression in animal models. The confirmation that depressed rats negatively affect healthy rats was in agreement with an earlier depiction of shared emotions between

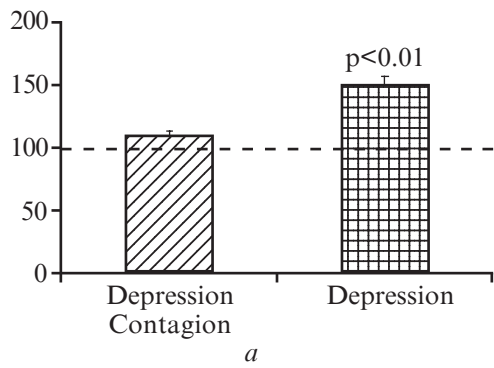
healthy and depressed pigs (Reimert et al., 2013).

Despite being talked about so frequently, the aftermath of depression is becoming scarily gigantic, claiming more casualties more than ever before with every passing day. The complexity with which humans interact does not render much help in dealing with depression and its influences systematically. So, an eventual comprehension of the mechanisms involved in animal depression could help us find a way of tackling human depression mechanisms, the ultimate goal being to establish a therapeutic response.

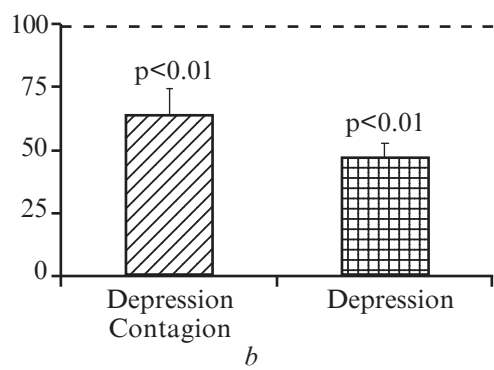
With limited pragmatism, we would hardly know the exact mechanism of infectious depression, but we could venture to advance cognizant and incognizant machinery as hypothetical happenings, with the incognizant action manifested by way of healthy rats' mimicry of depressed rats (Hatfield et al., 1994). The neuronal system and facial expressions are the most likely copied of the mechanisms (Ocampo & Kritikos, 2011), while communication would most likely define the conscious transfer of depression. A typical example of communication is co-rumination (Van Zalk et al., 2010).

Even though we established depression, there is an opposite effect on the other side of the experiment that is hardly ever given any attention, the positive impact. As observed in our findings, depressed rats became less depressed after spending five weeks cohabiting with healthy rats. Joiner (1994) examined college students and found that students infected their depressed counterparts with positive moods. The discovery revealed decreasing depressive feelings over a specified period. Consequently, as much as depressed individuals negatively impact the lives of those in their surroundings, healthy individuals offer the opposite effect on depressed patients. That healthy people are a form of medication is a massive boost to psychiatrists.

Immobility
(as a % of control group)



Climbing
(as a % of control group)



Defecation
(as a % of control group)

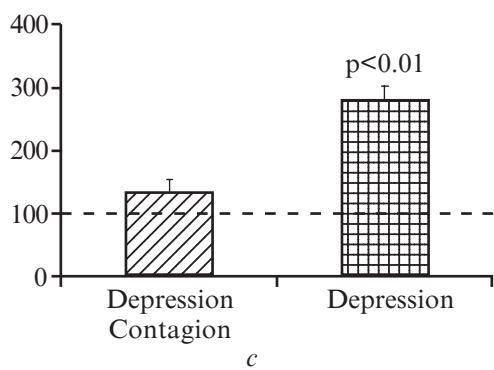


Fig. 4. Test for forced-swim parameters (Zeldets et al., 2018). We used the one-way ANOVA test for statistical analysis. Data shown as baseline percentages, conveyed as mean \pm SEM

Before we ran our test, we were unable to find any prior experimental models for evaluating depression in animals. This model makes our procedure the pioneer, and although it produced staggering results, it is not without its limitations. For all the significant differences shown between control rats and experimental groups, there are some undesired effects of our method. The inability to procure further testing with animals already subjected to forced-swim tests ranks as the most pertinent of concerns. Also, the lack of any domineering differences between the intake of water and glucose among the control and experimental groups means our protocol requires refinement. These results are not indicative of a profoundly depressed state in investigational groups. Nonetheless, it gives the world of investigative science a base for preliminary evaluation of depression and infectious depression in animals.

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Ключові слова: інфекційна депресія, гризуни, аналіз на афінність із сахарозою, тест із відкритим простором, тест із примусовим плаванням.

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CHANGES OF VEGETATIVE HEART TONUS AFTER INDUCTION OF GENERAL ANESTHESIA WITH MIDAZOLAM AND FENTANYL

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ИЗМЕНЕНИЯ ВЕГЕТАТИВНОЙ РЕГУЛЯЦИИ СЕРДЕЧНОГО РИТМА ПРИ ПРОВЕДЕНИИ ИНДУКЦИИ АНЕСТЕЗИИ МИДАЗОЛАМОМ И ФЕНТАНИЛОМ

Актуальность темы. Проведение индукции анестезии мидазоламом в сочетании с фентанилом часто приводит к гемодинамическим нарушениям, которые могут быть вызваны изменениями вегетативной регуляции деятельности сердца. В настоящее время отсутствуют исследования, посвященные изучению влияния индукции анестезии мидазоламом и фентанилом на вегетативную регуляцию сердечной деятельности.

Целью данного исследования было установление изменений вегетативной регуляции ритма сердца при индукции анестезии с использованием фентанила и мидазолама.

Материалы и методы. Было проведено проспективное рандомизированное исследование, одобренное этическим комитетом Государственного университета медицины и фармации имени Николая Тестемицану. Все участники дали

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