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Establishment of an animal model of depression contagion

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Abstract

Background—Depression is a common and important cause of morbidity, and results in a significant economic burden. Recent human studies have demonstrated that that depression is contagious, and depression in family and friends might cumulatively increase the likelihood that a person will exhibit depressive behaviors. The mechanisms underlying contagion depression are poorly understood, and there are currently no animal models for this condition.

Methods—Rats were divided into 3 groups: depression group, contagion group, and control group. After induction of depression by 5 weeks of chronic unpredictable stress, rats from the contagion group were housed with the depressed rats (1 naïve rat with 2 depressed rats) for 5 weeks. Rats were then subjected to sucrose preference, open field, and forced swim tests.

Results—The sucrose preference was significantly reduced in the depressed rats ($p < 0.01$) and contagion depression rats ($p < 0.01$). Climbing time during forced swim test was reduced in the depression and contagion depression groups ($p < 0.001$), whereas immobility time was significantly prolonged in only the depression group ($p < 0.001$). Rats in both the depression ($p < 0.05$) and depression contagion group ($p < 0.005$) had decreased total travel distance and decreased mean velocity in the open field test, whereas the time spent in the central part was significantly shorter in only the depression group ($p < 0.001$).

Conclusions—In this study, for the first time we demonstrated depression contagion in an animal model. A reliable animal model may help better understand the underlying mechanisms of contagion depression, and may allow for future investigations of the studying therapeutic modalities.

Keywords

Depression; Contagion; Rats; Animal model

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1. Introduction

Recent evidence suggests that psychiatric illnesses may be highly contagious [1]. Social contagion in humans is defined as a spread of affect, attitude or behavior from a target to recipient via social interaction, and can be occur when only one person experiences an event but the emotion is shared, facilitated through interaction with one another. As such, social relationships are an important component of mood, as emotional states are transferred from one person to another by way of mimicry and “emotional contagion”. Emotional states observed in others can be transferred over times frames that range from seconds to weeks [2].

Studies have focused mainly on the negative effects of emotional contagion, likely due to its significant consequences. The contagion of depressive symptoms has received much attention, as depression in family or friends might cumulatively increase the likelihood that a person will exhibit depressive behaviors. The phenomenon of contagious depression is well documented, and depression could have measurable long-term effects on another’s mood for three degrees of separation [3–6].

Depression is a common cause of morbidity; the lifetime incidence ranges from 13.3 to 17.1% in the United States [7]. According to the World Health Organization, depression ranks fourth on the list of global burden of diseases. Depression occurs in all genders, ages, in all social backgrounds and is associated with impaired health-related quality of life and social functioning [8–11], as well as with excess disability [12,13]. Depression can lead to suicide, with an estimated 850,000 lives lost each year [14]. Although conventional treatment of depression with antidepressant medications and cognitive behavioral therapy can be effective in up to 60–80% of patients, many patients do not have access to treatment. In others, the treatment may be limited by side effects to medicine or poor compliance [15]. Up to 40% of patients are resistant to treatment [14].

In addition to personal suffering, depression poses a significant economic problem. Depression requires chronic and costly treatment, and may result in lost work and early retirement [16]. Nearly half of lost productivity in the United States is due to major depression, with an estimated cost of $44 billion annually [17]. Depression is also associated with increased medical utilization, increased costs for other health conditions, worse long-term outcomes, and worse adherence to medication regimens [18].

Contagious depression is an interesting but poorly understood phenomenon. Currently there are no established animal models to study the underlying mechanisms, prevention, and treatment of contagious depression. In this study we tested for the first time the contagion hypothesis in an animal model. Specifically, we proposed that depressive behaviors could be induced in healthy rats after being exposed to depressed rats. Our goal was to document the existence of the contagion effect in rats and to determine whether it is specific to depressive symptoms or could be generalized to other mood disorders (e.g., anxiety). A better understanding of the mechanism underlying contagious depression may lead to the development of new therapeutic strategies.

2. Materials and methods

2.1. Experimental design

This study was conducted according to the recommendations of the Declarations of Helsinki and Tokyo and the Guidelines for the Use of Experimental Animals of the European Community. The Animal Care Committee at the Ben-Gurion University of the Negev approved the experiments.

Male Sprague-Dawley rats (Harlan Laboratories, Israel) were used in this experiment. Rats had no overt pathology and weighed between 300 and 350 g each. Rats were kept in cages, three rats per cage for at least 2 weeks after arrival to allow for adaptation. Rats were housed according to weight, age, and the size of the cage. Purina Chow and water were available ad libitum.

Before initiation of the experiment, 69 animals were tested for the presence of depressive behaviors using a 3-day sucrose preference test. Rats that did demonstrate sucrose preference were not included in the experiments. Furthermore, considering that all rats were housed as three rats per cage prior to beginning the experiment, rats that were housed in the same cage as the depressed rats were also excluded (to prevent possible contagion effect of depressed rats on their cohabitants). This test identified two “depressed” animals, and six rats in total were excluded according to the above criteria. Three additional rats, chosen at random, were excluded to reach a sample size of 60 rats that would be included in the “depression” group.

In addition to the 60 rats in the depression group, the remaining 60 rats were randomly divided into the contagion group or control group, with 30 rats in each group. Rats in the depression group were subjected to several manipulations of chronic unpredictable stress (CUS), as described below, to induce depression for the duration of 5 weeks. At the end of 5 weeks, rats were subjected to a sucrose preference test to determine whether they developed depression. After induction of depression in the depression group, preliminary tests were done to confirm the development of depression-like behavior (Fig. 1).

In the second part of the experiment 30 naive rats from the contagion group were added to the cages of depressed rats in a ratio 1:2 respectively (1 naive rat from the contagion group together with 2 rats from depressed group) for an additional 5 weeks. In total we created 30 social groups, with each group consisting of two depressed rats and one naïve rat. After 5 weeks of cohabitation (10 weeks from the initiation of the experiment), all groups were subjected to all behavioral tests described below in the following order: sucrose preference test, open field test, and forced swim test. During some behavioral tests, the rats were temporarily transferred to a single cage (i.e., in the sucrose preference test) or to another cage (i.e., during the CUS), but they were always afterward returned to their original social groups. All rats were numbered and marked throughout the experiment.

2.2. Inducing depression in rats by chronic unpredictable stress (CUS)

The depression model consisted of the following stressors in random order: grouped housing (six rats instead of three per cage for 18 h), placement in a tilted cage (45° along the vertical

axis for 3 h), food deprivation (18 h), water deprivation and exposure to an empty water bottle immediately following a period of acute water deprivation (18 h), placement in a soiled cage (300 ml of water spilled in the bedding) for 8 h, continuous lighting and reversed light/dark cycle for 48 h per week, and 5-min hot environment (40 °C). Rats were exposed to 2 of the 7 stressors daily in a random order; one in the daytime and second at night for 5 sequential weeks [19].

2.3. Sucrose preference test

The sucrose preference test was performed as described previously [20] with minor modifications. Before the start of experiment, after 5 weeks and after 10 weeks, rats were allowed to consume 1% (w/v) by placing two bottles of sucrose solution in each cage for 24 h. The rationale for the two bottles is that the appearance of an additional bottle in the rat's cage during the initial part of the sucrose preference test may frighten the rat. Afterwards, one of the bottles was replaced with water for 24 h. As such, this design may help avoid the effects of neophobia. Following the adaptation procedure, the rats were deprived of water and food for 12 h. The sucrose preference test was conducted at 9:00 a.m. The rats were housed in individual cages and given free access to the two bottles containing 100 ml of sucrose solution (1%, w/v) and 100 ml of water, respectively. After 4 h, the volume (ml) of both the consumed sucrose solution and water was recorded, and sucrose preference was calculated as sucrose preference (%) = sucrose consumption (ml)/(sucrose consumption (ml) + water consumption (ml)) × 100%.

2.4. Open field test

The open field test was performed as described previously [21]. The standard open field test is commonly used to assess locomotor, exploratory and anxiety-like behavior in laboratory animals, and behavioral responses to novelty. The open field test task approaches the conflict between the innate fear that rodents have for the central area of a novel or brightly lit open field vs. their desire to explore new environments. When anxious, the natural tendency of rodents is to prefer staying close to the walls (thigmotaxis). In this context, anxiety-related behavior is measured by the degree to which the rodent avoids the center of the open field. The open field is made of a black lusterless Perspex box (120 cm × 60 cm × 60 cm), which was divided into a 25% central zone and the surrounding border zone. Rats were placed in the corner of the open field facing the wall. The apparatus was situated in a dark room. Experiments were recorded by a video camera suspended approximately 200 cm above the open-field arena. 5% alcohol was used to clean the apparatus prior to the introduction of each animal. The rats' behavior (i.e., locomotor activity) was videotaped for 5 min by a Logitech HD Pro Webcam C920 camera with post-recording analysis performed using Ethovision XT software (Noldus, Wageningen, The Netherlands). Specifically, the following parameters were analyzed: total travel distance, travel distance in central part of the field, time spent in central part of the field, and mean velocity.

2.5. The forced swim test (FST)

The FST test is based on the observation that rats, when forced to swim in a restricted space from which they cannot escape, will eventually cease attempts to escape and become immobile apart from the small movements necessary to keep their heads above water. The

FST is a standard behavioral test for assessing depression in rodents (typically rats and mice) and is used to test the efficiency of antidepressant drugs. The test was performed as described previously [20]. Briefly, rats had an initial 15-min swimming session 24 h before euthanasia. This session was for training purpose with no data collection. After the first 15-min swim sessions, the rats were removed from the cylinders, dried with paper towels, and placed in heated cages for 15 min. Afterwards, they were returned to their cages. On the day of euthanasia, a 5-min test was performed and behavior was digitally recorded for assessment. FST was conducted by placing rats in individual glass cylinders (100 cm tall and 40 cm in diameter) containing room temperature water at a depth of 40 cm. After the 5-min test, the rats were dried and euthanized. Experiments were videotaped for post-recording measurements of the duration of immobility periods. As in previous tests, three independent researchers blind to the experimental group performed the assessment.

2.6. Statistical analysis

Statistical analysis was performed with the SPSS 18 package (SPSS Inc., Chicago, IL, USA). Parametric methods will be used unless otherwise specified. The Kolmogorov–Smirnov test was used to determine the pattern of distribution in groups taking into account the number of rats in each group for choosing the appropriate tests for the comparisons between the different parameters. The significance of comparisons between groups for non-parametric data and parametric data with abnormal distribution was determined using the Kruskal–Wallis followed by Mann–Whitney tests. One-way ANOVA with Bonferroni post hoc test or Student's t-tests and two-tailed tests were used for parametric data with normal distribution. Results were considered statistically significant when $p < 0.05$ and highly significant when $p < 0.01$.

3. Results

3.1. Sucrose preference test

The sucrose preference data demonstrated that both the depression group and depression contagion group exhibited depressive behaviors after five weeks of exposure to the chronic unpredictable stress or cohabitation with depressed rats, respectively (Fig. 2). The percent of sucrose preference was significantly reduced in the 60 depressed rats compared to the 30 rats in the control group following 5 weeks after the onset of CUS (68 ± 2% vs. 83 ± 3% $p < 0.01$) (Fig. 2). In the two groups, 60 depressed and 30 depression contagion rats demonstrated a statistically significant difference in the percent of sucrose preference at 10 weeks compared to the 30 rats in the control group (73 ± 2% and 73 ± 3% $p < 0.01$ vs. 84 ± 2%) (Fig. 2).

3.2. Forced swimming test

The immobility time during the forced swim test was prolonged in both groups, but only in the depression group was there a significant difference ($p < 0.001$) compared to the control group (Fig. 3A). The climbing time during the forced swim test was significantly reduced in both the depression and contagion depression groups ($p < 0.001$) compared to the control group (Fig. 3B).

3.3. Open field test

Behavior parameters in the open field test are presented in Fig. 4. Rats in both the depression group and depression contagion group had a decreased total travel distance (depression contagions $p < 0.05$ and depressed $p < 0.005$, Fig. 4A), and a decreased mean velocity (depression contagions $p < 0.05$ and depressed $p < 0.005$, Fig. 4C) compared to the control group. The time spent in the central part was shorter in the depression group ($p < 0.001$) however in the contagion depression group this difference did not reach statistical significance (Fig. 4B).

4. Discussion

In this study we demonstrated that healthy rats, similar to humans, developed depressive-like behaviors when housed for long periods with depressive rats. For the first time, we established an animal model of contagion depression. According to the behavioral tests (Figs. 2–4), naive rats developed contagion depression after 5 weeks of cohabitation in the same cage with the depressed rats.

Our findings were in line with the limited human studies. Roommates of depressed college students became more depressed themselves over the course of the 3-week study; these findings were specific to depressed symptoms [4]. Dating couples and spouses living together also experienced similar levels of depressive symptoms [22,23]. Children of depressed parents experienced an increase in depressive symptoms following the elevations in their parents' depressive symptoms [24]. The literature suggests that if a person's friends or family are depressed, this might cumulatively increase the chance of the person developing depression. This depression could have measurable long-term effects on the moods of his or her contacts for three degrees of separation [3]. To the best of our knowledge, this is the first study that examined the contagion effect in rats. One previous study in pigs suggested that pigs might be sensitive to emotional contagion, which could have implications for the welfare of group-housed pigs [25].

In this study, depression in rats in the depression group was induced by the chronic unpredictable stress (CUS). This model, which mimics socio-environmental stressors in everyday life, is one of the most well documented and extensively used animal models of depression, which results in depressive-like behavioral effects similar to symptoms observed clinically. Rats subjected to the CUS paradigm for several weeks can exhibit almost all demonstrable depressive symptoms [26]. CUS is a dependable depression model with high face, predictive and construct validity (Forbes et al., 1996; Moreau, 1997). It is also one of the animal depression models for analyzing cellular and molecular mechanisms underlying the pathophysiology of depression and for exploring the mechanism of antidepressants (Sikiric et al., 2000; Zhou et al., 2005; Banasr et al., 2007; Bachis et al., 2008; Bondi et al., 2008).

With this model rats from the depression group exhibited depressive behaviors after 5 weeks and continued to be depressed by the end of the experiment (10 weeks). This was confirmed by the sucrose preference and forced swim tests (Figs. 1–3). The behavioral tests chosen for this study reflect a wide spectrum of behavioral abnormalities. The sucrose preference and

forced swim test were employed to assess depression-like behavior [19]. The open field test was used to determine the emotional profile of rats [27]. This test is also frequently used in the behavior studies in depressed rats [28–34]. The precise mechanism of contagion is not known, but it likely has both unconscious and conscious elements. The unconscious element could relate to automatic mimicry [35], copying of emotionally relevant bodily actions, particularly facial expressions, seen in others and the mirror neuron system [36]. Through afferent feedback, the receiver feels the sender's expressions, and this leads toward emotional convergence [35]. The conscious component could be due to shared communication styles such as co-rumination [37].

Regarding the symptom specificity of the contagion effect, it is important to note that specificity can take three forms. First, contagion may be specific to depression within symptoms. That is, depression may lead to depression in a partner, whereas anxiety may not lead to anxiety in a partner (i.e., within-symptom specificity). Second, contagion may be specific to depressed symptoms in that depression leads to partner depression but anxiety does not lead to partner depression (i.e., specificity of cause). Third, contagion may be specific to depression in that depression leads to partner depression but does not lead to partner anxiety (i.e., specificity of consequence).

In the main-effect analyses, contagion was specific to depressed symptoms vs. anxious symptoms and negative affect; however, lowered positive affect (i.e., anhedonia) was not contagious [4]. These results suggest that anhedonia in itself is not sufficient to induce the contagion effect, and the other symptoms of depression also seem to be required. However, it was the symptoms of depression, and not those of anxiety or general negative affect, that induced the depressive behaviors [4].

An interesting finding in our study was that the rats from the depressed group after 5 weeks of cohabitation with naive rats became a little less depressed than was observed after CUS. A similar finding was found in humans: in college roommates, high reassurance seeking roommates of non-depressed targets became somewhat less depressed (and anxious) over the course of the study [4]. This suggests that the contagion effect can be bi-directional. Depressed subjects can influence the healthy subjects, and healthy, non-depressed subjects can positively influence the emotional state of the depressed subjects. This finding can be useful in the treatment of depressive disorders. If the pattern of emotional contagion were similar to the transmission of infectious disease, one might increase a person's emotional resilience similar to how one could boost immunity levels against infectious diseases. In this way, new preventative strategies in psychiatry would target populations as well as individuals.

One pragmatic aim is to encourage greater contact with those network members who have a positive effect on the patient's mood. Therapeutic intervention is directed at shared activities that have a beneficial effect on the overall functioning of network groups. For instance, pleasant activity scheduling, as part of behavioral activation, would be more meaningful if the patient's supportive social network is incorporated in the activities. The importance of positive support in depression treatment is vital, especially from social contacts beyond the immediate family.

Mental disorders such as depression and anxiety are difficult to replicate in a laboratory animal. At the same time, no animal model is able to fully mimic any mental illness, as these are characterized by specific disturbances in functions that are absolutely unique to humans. However, a general approach is to reproduce particular symptoms of mental diseases in laboratory animals or to develop models to identify novel compounds as potential treatments. In our experimental paradigm, during periods of long cohabitance, hierarchy may be an important factor to consider in animal social groups. It would be difficult if not impossible to avoid this situation in social animals when housing several individuals together, and our experiment's methodology required the formation of social groups. Although we did not specifically study this phenomenon, we did not observe even a single injury inflicted by dominant rats to submissive ones.

Despite significant advancement in understanding the mechanisms of depression and the development of treatment strategies, depression remains a life-threatening condition that is associated with a considerable mortality and morbidity. Until recently, the social transmission of mood and behavior has been hard to study. The complex and dynamic nature of human relationships makes it difficult to quantify the effect of mood contagion at a population level. Animal models of contagion may help to better understand the mechanisms of this unique phenomenon and to develop therapeutic strategies.

5. Conclusions

Although contagion depression in humans has been described by numerous studies, this condition is poorly understood. Animal models of contagion depression have not yet been established. Animal models are an important tool for investigating the mechanisms underlying various diseases, for testing new strategies and methods of treatment, and to evaluate the potential efficacy of therapeutic interventions. Thus, valid animal models of contagion depression can have significant implications allowing further investigations of the pathophysiology and treatment of this disorder.

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HIGHLIGHTS

- Healthy rats developed depressive-like behaviors when housed for long periods of time with depressive rats.
- The method used in this study can be used as an animal model of contagion depression.
- According to the behavioral tests, naive rats developed contagion depression after 5 weeks of cohabitation in the same cage with the depressed rats.

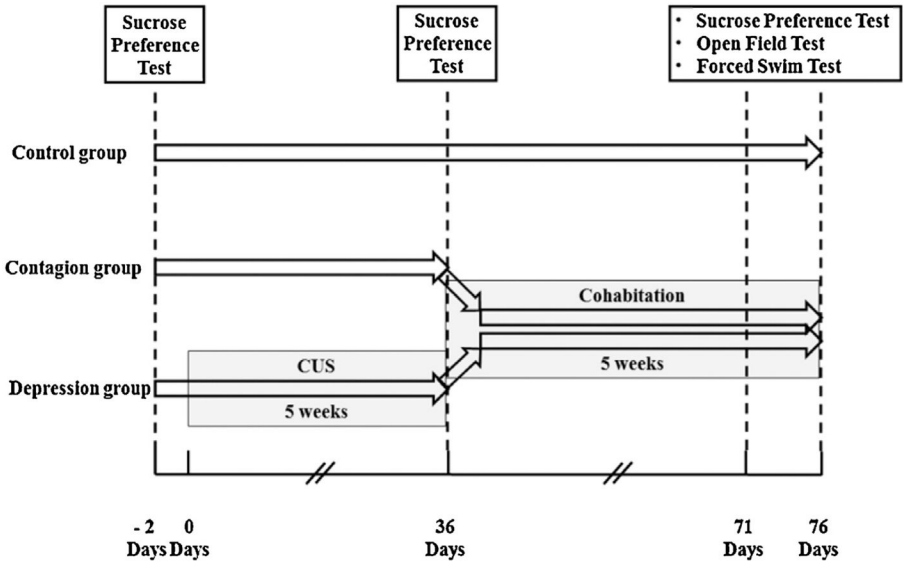

Fig. 1.

Experimental design. 69 rats animals were tested for depressive behaviors on days −2 to 0 using a sucrose preference test. After exclusion of nine rats (see text for details), 60 rats were included in the depression group. An additional 30 rats were included in the contagion group and 30 in the control group. Rats in the depression group were subjected to several manipulation of chronic unpredictable stress (CUS) for 5 weeks, after which all rats were subjected to a sucrose preference test. Rats in the contagion group were then housed with depressed rats (1 naïve rat with 2 depressed rats) for 5 weeks, after which all groups were subjected to sucrose preference test, open field test, and forced swim test.

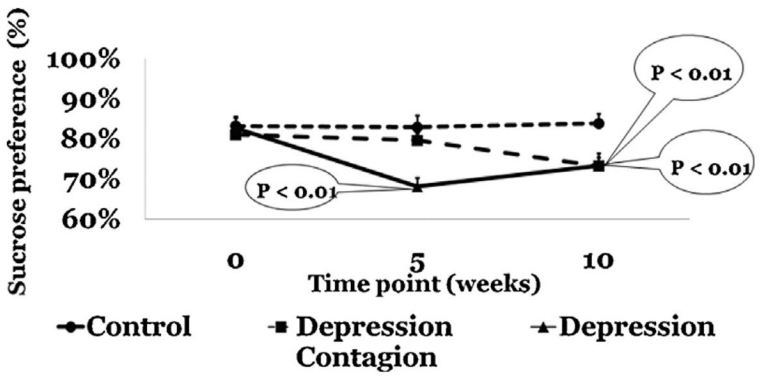

Fig. 2.

Behavior parameters in the sucrose preference test. The percent of sucrose preference was significantly reduced in the 60 depressed rats compared to the 30 rats in the control group following 5 weeks after onset CUS (68 ± 2% vs. 83 ± 3% $p < 0.01$, Fig. 3). In both groups, 60 depressed and 30 depression contagions rats demonstrated a statistically significant difference in the percent of sucrose preference at 10 weeks compared to the 30 rats in the control group (73 ± 2% and 73 ± 3% $p < 0.01$ vs. 84 ± 2% Fig. 3). In the sucrose preference test, one-way ANOVA with Bonferroni's post hoc test was used.

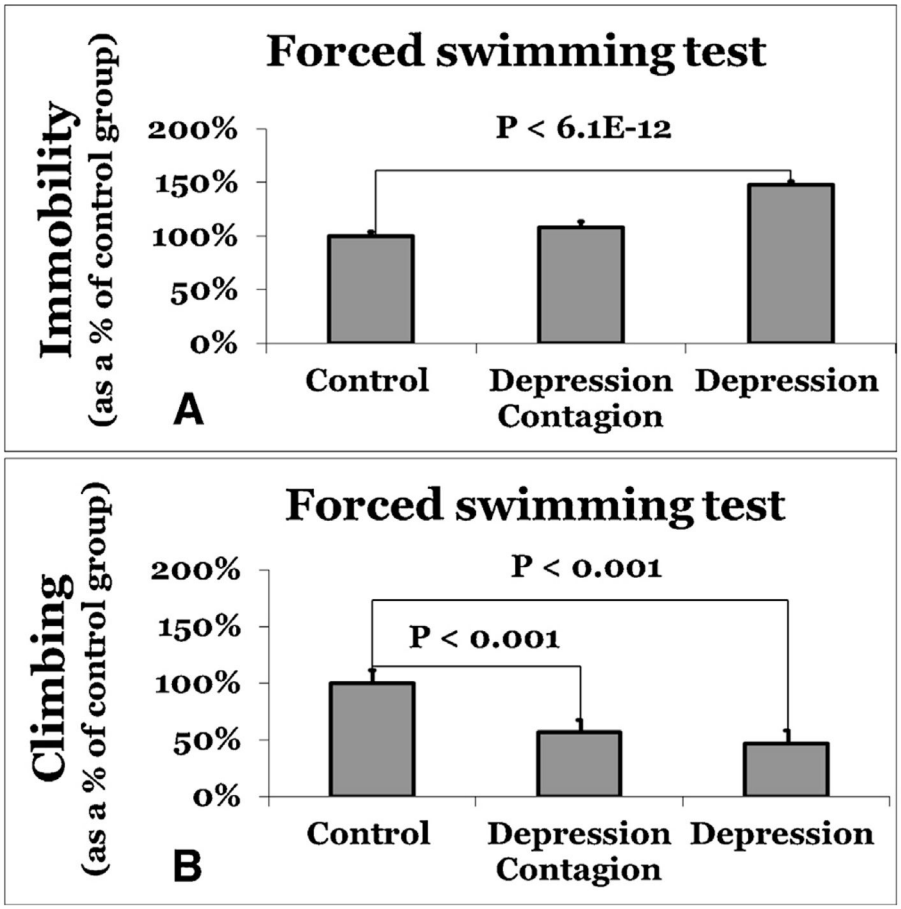

Fig. 3.

Behavior parameters in the forced swim test. The depressed and depressed contagions rats had elevated immobility time but only in the depressive group was there a significant difference (148 ± 3% $p < 6.1E–12$, and 109 ± 6% Fig. 2A), compared to the 30 rats in the control group. 60 depressed and 30 depressed contagions rats had a decreased climbing time (47 ± 11% $p < 0.001$, and 56 ± 11% $p < 0.001$, Fig. 2B). The FST data are presented as percent of the control group (one-way ANOVA followed by Bonferroni's post hoc test).

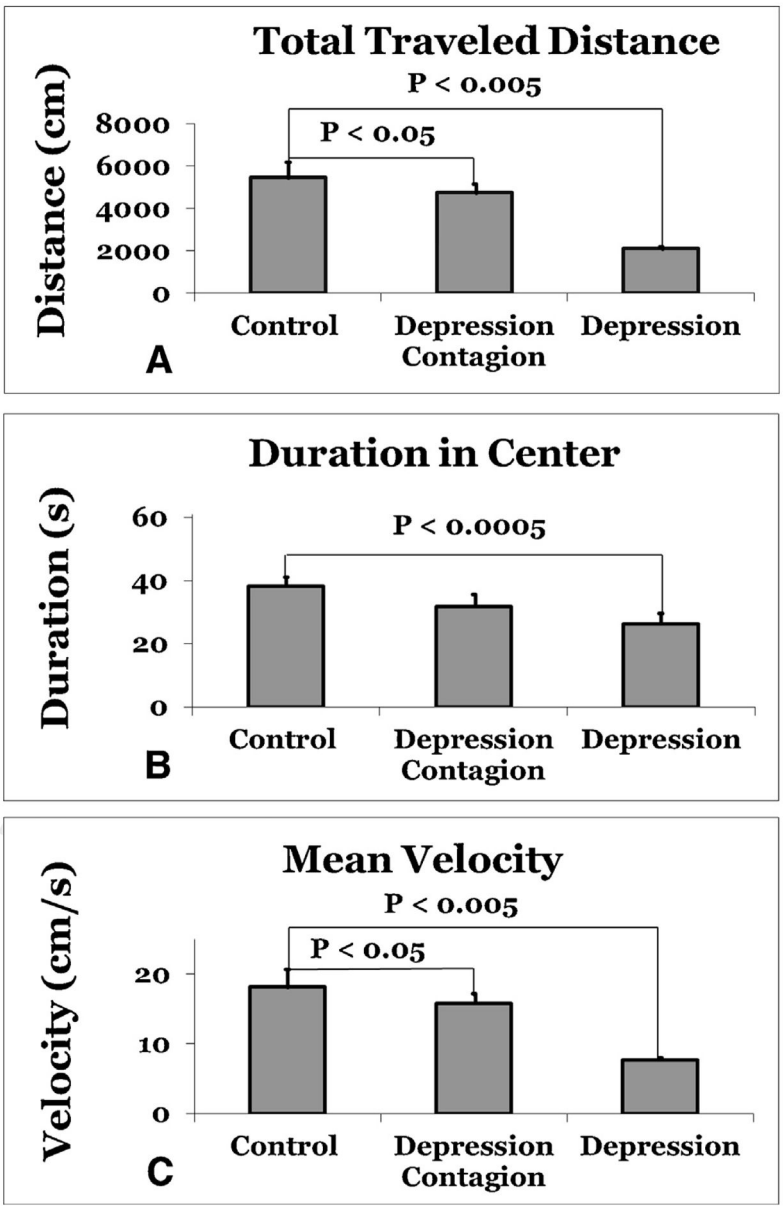

Fig. 4.

Behavior parameters in the open field test. 30 depression contagions and 60 depressed rats had a decreased total travel distance (4753 ± 383 cm $p < 0.05$ and 2095 ± 98 cm $p < 0.005$ vs. 5452 ± 758 cm, Fig. 3A). The depression contagion rats and depressed rats spent less time in the central part of the field (31.8 ± 3.5 s p N.S. and 26.4 ± 3.3 s $p < 0.0005$ vs. 38.4 ± 2.6 s, Fig. 3B) and had a decreased mean velocity (depression contagions 15.8 ± 1.3 cm/s $p < 0.05$ and depressed 7.7 ± 0.3 cm/s $p < 0.005$ vs. 18.2 ± 2.5 cm/s, Fig. 3C). In all 3 tests, the Kruskal–Wallis followed by Mann–Whitney test was used.