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Correlation among the Behavioral Features in the Offspring of Morphine-Abstinent Rats

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Original Article

Abstract

Background: Critical analysis of new evidence in medical sciences relies on statistics in terms of correlation. The aim of the present study was to evaluate the correlation coefficients among the behavioral features in the offspring of morphine-abstinent parent(s).

Methods: The offspring of various types of parental morphine-exposure were divided into 4 groups including offspring of healthy parents (CTL), offspring of paternal morphine-abstinence (PMA), offspring of maternal morphine-abstinence (MMA), and offspring of both morphine-abstinence (BMA). Pain perception, depression-like behavior, and avoidance memory in the offspring were quantified. The logical structure of association was measured using the Pearson correlation analysis.

Findings: A strong correlation was observed between pain and depressive-like behavior in female and male offspring of healthy parents. Moreover, in the male and female offspring of healthy parents and BMA, no significant correlation was observed between avoidance memory and pain behavior or depressive-like behavior. However, in the offspring of MMA, a strong correlation was observed between avoidance memory and depressive-like behavior.

Conclusion: The results of the study signified the importance of correlation analysis in addictive behavior. The results revealed that the pattern of correlation of the behavior of the offspring of MMA and PMA differed.

Keywords: Correlation study; Administration; Epigenetic; Behavior; Morphine

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Introduction

Opioids, such as morphine, oxycodone, codeine, and methadone, are a group of drugs that are effective in the treatment of moderate to severe pain.[1,2] Although, chronic use of opioids leads to dependence, and consequently, to many medical, economic, and social problems.[1,3]

Drug addiction is a disorder that results from the interaction of environmental and genetic factors.[4] Moreover, epigenetics play an important role in the maintenance and development of addiction.[4] Vassoler et al. found that the transgenerational effect of parental exposure continues even in the absence of the opioid.[5]

Long-term use of morphine may change the behavior and brain structure of individuals. Both chronic use by the individual and parental addiction have a severe impact.[6] Parental morphine exposure may lead to depression-like behavior and addiction vulnerability.[6] Furthermore, parental morphine exposure may lead to neurochemical changes such as downregulation of the dopamine receptor gene and dendritic retraction.[3,7-9] Previously, we found that parental morphine-exposure significantly changed pain perception, depressive-like behavior, and avoidance memory in the offspring.[10]

Furthermore, in scientific researches, female animals are not included in the experiments due to their reproductive cycle and hormonal secretion that may generate experimental variability. Thus, the scientific basis for medical advice is based on data collected from male animal models. For this reason, personalized medicine for females is limited. However, recent results revealed that females rats are not more variable than male rats, but still researchers are focused on male animals due to their concern about female variability.[11,12] Hence, in this study, we have evaluated the response of both genders to parental morphine exposure.

Furthermore, the accumulative evidence showed that pain, memory, and depression are strongly correlated. For instance, pain is strongly associated with anxiety and depressive disorders.[13] Moreover, working memory is strongly associated with daily pain and movement-evoked pain.[14]

Moreover, the long-term use of opioids in adults has increased and it is urgent to understand the impact of parental morphine exposure on the offspring.[15-17] Previously, we reported that parental morphine-exposure significantly changes pain perception, avoidance memory, and depressive-like behavior in both sexes of offspring.[18] Moreover, neither the correlation between chronic pain and depression, nor their pathophysiological mechanism has been determined as a result of which the treatment of depression accompanied by pain remains an enormous challenge.[19]

Critical analysis of new evidence in medical sciences requires extensive medical knowledge for research and interpretation which rely on statistics.[20] It is important to emphasize statistical significance by considering the effect of sample size and whether the differences are clinically meaningful.[20] Scientific hypotheses are stated in terms of correlation or absence of correlation and the practical results of correlational studies can test the evidence under experimental conditions.[21,22]

Correlation is a statistical technique to evaluate the possible association between two variables. The correlation is measured using a correlation coefficient, which represents the strength between the variables. The coefficient value is within the range of -1 to +1 and correlation coefficients closer to ±1 are the stronger correlations. The positive value indicates that the variables are directly related and the negative value indicates that the variable is inversely related.[23] The findings of correlational researches are used to forecast events using current knowledge and data, although adequate prudence is required when using the correlation method for data analysis.[24]

Although correlational analysis has been well studied in statistical science, there is a lack of studies on the application of this analysis in the field of addictive behavior. According to our knowledge, the current study is the first study on the correlation between future behavioral variation and exposure to drug abuse. The results of the study will assist in the development of treatment for addictive behaviors in drug-addicted individuals and their offspring. Thus, the aim of the study was to evaluate the correlation coefficients among pain, memory, and depressive-like behaviors in the rat offspring of morphine-abstinent parent(s).

Methods

Adult Wistar albino rats, weighing 220-250 grams

at the beginning of the experiment, were used. The rats were housed in plexiglass cages (4 rats per cage) in a room with 12hour/12hour light-dark cycle (7:00 am to 19:00 pm) with free access to food and water at a constant temperature of 22 ± 2 °C. In this study, a total of 64 males and females were used for mating and morphine exposure. Furthermore, 128 male and 128 female offspring were used for the experiments (8 female × 8 male 4 × 4 groups of offspring × 4 experiments). A total of 320 animals were used in the current study. The female offspring were tested on the diestrous phase of the estrous cycle. Moreover, all experimental procedures were performed according to the guideline for the use and care of animals provided by the sciences ethics committee at the Tehran University of Medical Sciences, Tehran, Iran.

According to our previous study, morphine abstinence in rats was induced by dissolving morphine sulfate (Temad Co., Tehran, Iran) in their drinking fluid.[4] Sucrose 2% (Merck & Co., Kenilworth, NJ, USA) was added to the drinking fluid to mask the bitter taste of morphine. Naloxone hydrochloride (Sigma-Aldrich Corporation, St. Louis, MI, USA) was dissolved in 0.9% saline and was injected intraperitoneally to approve morphine dependence.

According to a modified protocol by Akbarabadi et al., 24 male and 24 female Wistar rats received oral morphine sulfate.[4] Morphine concentration was increased from 0.1 to 0.3 mg.ml^{-1} in the interval of 48 hours. Finally, a concentration of 0.4 mg.ml^{-1} of morphine was administrated for 15 days. Naloxone was administrated to all the animals to confirm withdrawal syndrome. The withdrawal symptoms were observed and recorded to confirm that the rats are in the morphine abstinence state. The schematic diagram of morphine treatment is presented in figure 1.

The rats were randomly assigned for mating 10 days after the last morphine administration. The offspring were arranged in 4 groups; offspring of healthy parents (CTL), offspring of maternal morphine-abstinence (MMA), offspring of paternal morphine-abstinence (PMA), and offspring of both morphine-abstinence (BMA). For each experiment, 16 offspring (8 females and 8 males) in each group were used. In total, 66 rats (4 tasks × 16 replications) were used in each group.

The impact of parental morphine exposure on avoidance memory was measured using passive avoidance memory task.[4] The apparatuses that were used for the task consisted of 2 dark and light compartments (25 × 25 × 20 cm). The compartments were separated by a guillotine door. The dark compartment was fitted with an electric shock provider via a grid floor. In the learning trial, the animals were separately placed in the light compartment with the door kept open and the animals were free to explore the compartment for 3 minutes. The rats were trained on the second day. For this purpose, the animal was acclimatized to the laboratory environment for 30 minutes, and then, was placed in the light compartment. After 5 seconds, the door was lifted, and when the animals crossed with all four paws into the dark compartment, the door was closed and an electric shock was delivered to the gird floor (50 Hz, 1 mA, and 5 seconds). The animals were taken out of the compartment and transferred to their home cage for 2 minutes.

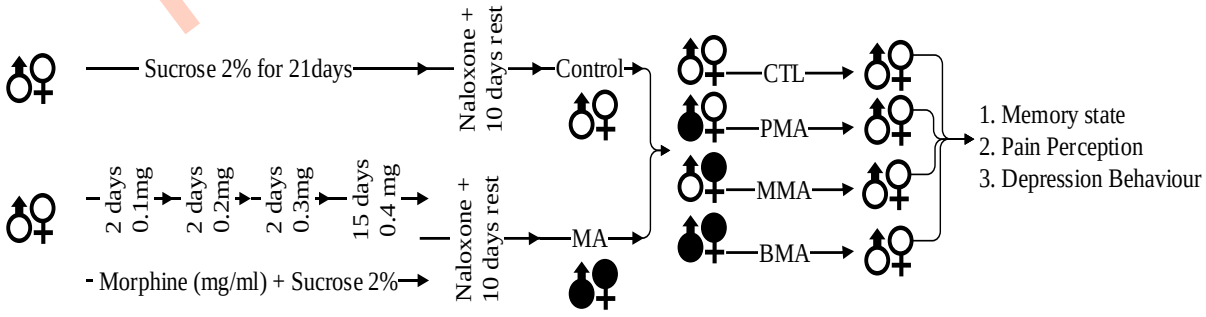

Figure 1. The schematic diagram of morphine exposure, mating, and experiments in the animal model
After morphine exposure, the offspring of morphine-abstinence (MA) were used for mating and the offspring were divided into offspring of maternal morphine-abstinence (MMA), offspring of paternal morphine-abstinence (PMA) and offspring of both morphine-abstinence (BMA). The experiments were conducted on the offspring of the different groups.

The successful acquisition of avoidance memory within 120 seconds was recorded in case of no entrance into the dark compartment. Otherwise, the learning trial was repeated. The animals without successful acquisition were omitted from the study. In the test trial, animals were separately placed in the light compartment and the door was opened after 5 seconds. The step-through latency for crossing into the other compartment was recorded. The testing trial was ended when the animal remained in the light compartment for 300 seconds or the animal entered into the dark compartment. In the test trial, the electric shock was not delivered to the gird floor.

The open-field test is known to evaluate anxiety and depression-like behavior.[25,26] Locomotor activities such as rearing and grooming stand for the tendency of animals to explore their surrounding environment. Change in locomotor activity is a standard for depressive-like behavior.[27] The open-field apparatus consisted of a plexiglass square box (35 × 35 × 40 cm). Each animal was placed at the center of the apparatus and left free to move for 10 minutes. The number of times that the animal reared up on its hind paws was recorded as rearing. The number of times that the animal preened its tail or fur with its forepaw or mouth was recorded as grooming. Moreover, the number of times that the animal passed the square-cross was recorded as locomotion.

Forced swimming test is another behavioral test for the evaluation of depression-like behavior in rodents.[28] After the open-field test, the animals underwent the forced swimming test. For this purpose, each rat was placed inside a plexiglass cylinder (60 × 30 cm) with a video camera recording from above the cylinder. The cylinder was filled with purified water and the temperature was adjusted to 25 °C. In this experiment, each animal was left in the water and allowed to swim for 5 minutes. The latency to immobility and the total time of immobility in the water was measured. Immobility in the forced swimming test is an index for depression-like behavior.[29,30]

The writhing test is a method for the evaluation of visceral pain.[31,32] In this method, acetic acid (Merck & Co., Kenilworth, NJ, USA) was injected into the peritoneum to induce visceral pain. For this purpose, the rats were habituated in a small chamber. After 10 minutes of observation, the rats received 10 $ml.kg^{-1}$ acetic acid (0.08%) in the peritoneum. The perception of visceral pain was characterized by abdominal contraction, which is known as writhing. The rats were adjusted for 5 minutes. The number of writhing episodes and the total time of writhing was recorded for over 10 minutes.[33]

Acute and chronic pain were measured using the formalin test.[34,35] For this purpose, in each rat, pain was induced by the application of 100µl formalin 2.5% (Merck & Co., Kenilworth, NJ, USA) on the dorsal surface of the hind paw. The rat was placed in an observation chamber that had 3 mirrors on different sides to allow a clear view of the paws. The total time that each rat spent licking the paw was recorded. The acute pain induced by direct stimulation of the nociceptor was observed up to 10 minutes after formalin injection. Persistent pain was observed 20-40 minutes after formalin injection.

The logical structure of the association between variables was measured using correlational analysis. For this purpose, the values were subjected to Pearson correlation analysis using SPSS software (version 23, IBM Corporation, Armonk, NY, USA). All P-values lower than 0.05 were considered as significant. The figures were drawn in MS Excel 2013 (Microsoft Coporation, Redmond, WA, USA).

Results

Avoidance Memory

Healthy parents: Results of Pearson analysis showed that there was no significant correlation between avoidance memory and pain behavior or between avoidance memory and depressive-like behavior in the CTL group (Table 1).

Morphine Abstinent parent: The results showed that avoidance memory had a significant correlation with depressive-like behaviors in female offspring of PMA (Table 2). Furthermore, the results revealed that avoidance memory had a significant correlation with depressive-like behavior in female offspring of MMA (Table 3).

The results revealed a positive correlation between avoidance memory and the immobility feature in depressive-like behavior in female offspring of PMA ($R = 0.713$, $P < 0.05$). The results suggest that with an increase in the immobility feature of depressive-like behavior in the female offspring of PMA, avoidance memory was strongly increased (Figure 2, A).

Table 1. Summary of the significant difference in the offspring with different parental morphine-exposure

Behavior	Expriment	Female			Male		
		MMA	PMA	BMA	MMA	PMA	BMA
Avoidance Memory	Memory in passive avoidance test	↓	↓	↓	↓	↓	↓
Depression-like behavior	Locomotion in open field test	↑	–	↑	↓	↓	↓
	Rearing in open field test	–	↓	–	↓	↓	↓
	Grooming in open field test	–	–	–	–	–	–
	Latency in the forced swimming test	–	–	–	↓	↓	↓
	Immobility in the forced swimming test	–	–	↑	↑	↑	↑
Pain Perception	Total time of writhing in the acetic acid test	↓	–	↓	↓	↓	↓
	Total number of writhing episodes in the acetic acid test	↓	↓	↓	↓	↓	↓
	Acute pain in the formalin test	–	–	–	↓	↓	↓
	Persistent pain in formalin test	–	–	–	–	–	↓

The results presented in the table are from our previous study and represent the significant changes in parental morphine-exposed offspring.[10] The female and male offspring were divided into three distinct groups, offspring of maternal morphine-abstinence (MMA), offspring of paternal morphine-abstinence (PMA), and offspring of both morphine-abstinence (BMA). The significant increase was represented with (↑) sign, significant decrease was represented with (↓) sign, and no significant difference was represented with (–) sign.

The results showed that avoidance memory in female offspring of PMA has a strong negative correlation with latency feature in depressive-like behavior ($R = -0.806$, $P < 0.05$). In the female offspring of PMA, with an increase in the latency feature of depressive-like behavior, avoidance memory was strongly decreased (Figure 2, B)

Results revealed a strong positive correlation between avoidance memory and total time of writhing in pain perception in the female offspring of MMA ($R = 0.911$, $P < 0.01$). In addition, in the female offspring with MMA, avoidance memory increased with an increase in the total time of writhing in pain perception experiment (Figure 2, C)

Moreover, a significant strong positive correlation was observed between avoidance memory and locomotion characteristics in depressive-like behavior in the male offspring of MMA ($R = 0.769$, $P < 0.05$). In the male offspring of MMA, an increase in locomotion feature of depressive-like behavior resulted in a strong increase in avoidance memory (Figure 2, D). Furthermore, avoidance memory in male offspring of MMA had a significant strong positive correlation with the rearing feature of depressive-like behavior ($R = 0.800$, $P < 0.05$) (Figure 2, C). An increase in the rearing feature of depressive-like behavior resulted in a strong increase in avoidance memory (Figure 2, D).

The results of Pearson analysis showed that there was no significant correlation between avoidance memory and pain perception or depressive-like behavior in the male and female offspring of BMA (Table 4).

Pain Perception and Depressive-like Behavior

Healthy parents: A significant correlation was observed between pain perception and depressive-like behavior in the offspring of different morphine-abstinent parents. However, the correlation differed in different genders depending on their parental morphine exposure.

Results showed that, in the female offspring in the CTL group, acute pain was correlated with the grooming feature of depressive-like behavior ($R = 0.715$, $P < 0.05$). An increase in the total number of grooming episodes in depressive-like behavior caused an increase in the perception of acute pain (Figure 3, A).

In contrast, in the male offspring in the CTL group, acute pain was correlated with the rearing feature in depressive-like behavior ($R = 0.711$, $P < 0.05$). The findings suggest that with an increase in the total number of grooming episodes, the perception of acute pain was increased (Figure 3, B).

Moreover, in the female offspring in the CTL group, latency feature in the depressive-like behavior had a strong negative correlation with the total number of writhing episodes in pain perception ($R = -0.813$, $P < 0.05$). The result suggest that with an increase in the latency feature of depressive-like behavior, the prevalence of writhing in pain behavior was strongly decreased (Figure 3, B).

Table 2. Pearson correlation coefficients in the female offspring (left border) and male offspring (right border) of healthy parents (CTL)

Memory	Time	Memory	Depression					Pain			Male	
		Time	Locomotion	Rearing	Grooming	Latency	Immobility	Persistent	Acute	Total Time	Total Number		
		1	-0.067	-0.318	0.525	0.057	-0.108	0.116	-0.070	-0.166	-0.539	Time	Memory
Depression	Locomotion	-0.043	1	0.621	-0.299	-0.807*	0.503	-0.403	0.697	0.403	0.231	Locomotion	Depression
	Rearing	0.485	0.729*	1	-0.846**	-0.439	0.146	0.052	0.711*	0.225	0.332	Rearing	
	Grooming	-0.301	0.097	-0.261	1	-0.029	0.245	-0.073	-0.440	-0.131	-0.436	Grooming	
	Latency	0.162	-0.639	-0.603	0.318	1	-0.832*	0.381	-0.650	-0.232	0.037	Latency	
	Immobility	-0.238	0.581	0.510	-0.443	-0.974**	1	-0.383	0.506	0.398	0.030	Immobility	
Pain	Persistent	-0.024	0.391	0.210	0.152	0.109	-0.062	1	-0.050	-0.229	0.023	Persistent	Pain
	Acute	-0.307	-0.028	-0.049	0.715*	0.221	-0.330	0.205	1	0.062	-0.088	Acute	
	Total Time	-0.669	0.527	0.130	-0.241	-0.713*	0.811*	0.070	-0.22	1	0.823*	Total time	
	Total Number	-0.642	0.370	0.189	-0.236	-0.813*	0.855**	-0.142	0.010	0.880**	1	Total number	
Female		Time	Locomotion	Rearing	Grooming	Latency	Immobility	Persistent	Acute	Total Time	Total Number		
		Memory			Depression					Pain			

**Significant correlation at the 0.01 level, *Significant correlation at the 0.05

Significant internal correlation was observed among features of depressive behavior in male (r = -0.807, r = -0.846, r = -0.832) and female (r = 0.729, r = -0.974) offspring. Moreover, significant internal correlation was observed among features of pain behavior in male (r = 0.823) and female (r = 0. 880) offspring. The red color illustrates a significant correlation between pain and depression in male (r = 0.711) and female (r = 0.715, r = -0.713, r = -0.813, r = 0.811, r = 0.855,) offspring. The results showed that avoidance-memory has no significant relationship with pain and depressive-like behavior. Moreover, a significant correlation was observed between pain and depressive-like behavior in both genders.

Table 2. Pearson correlation coefficients in the female (left border) and male offspring (right border) of paternal morphine-abstinence (PMA)

		Memory	Depression					Pain				Male	
		Time	Locomotion	Rearing	Grooming	Latency	Immobility	Persistent	Acute	Total Time	Total Number	Time	Memory
Memory	Time	1	-0.22	0.448	-0.186	0.193	-0.438	-0.322	-0.21	0.462	0.341		
Depression	Locomotion	0.019	1	-0.037	-0.298	-0.299	0.581	-0.276	-0.35	0.014	0.070	Locomotion	Depression
	Rearing	-0.124	0.341	1	-0.256	0.398	-0.226	-0.004	0.478	0.615	-0.002	Rearing	
	Grooming	-0.516	0.085	-0.318	1	0.312	-0.378	-0.300	-0.06	0.078	0.509	Grooming	
	Latency	-0.806*	-0.300	-0.025	0.240	1	-0.888**	-0.578	-0.180	0.647	0.443	Latency	
	Immobility	0.713*	0.251	0.196	-0.295	-0.946**	1	0.545	0.268	-0.553	-0.510	Immobility	
Pain	Persistent	0.308	0.242	0.282	-0.101	-0.481	0.662	1	0.767*	-0.680	-0.886**	Persistent	Pain
	Acute	-0.387	0.631	0.767*	0.035	0.231	-0.168	0.169	1	-0.123	-0.553	Acute	
	Total Time	-0.106	-0.348	-0.781*	0.323	0.028	-0.032	-0.126	-0.785*	1	0.713*	Total Time	
	Total Number	-0.309	-0.742*	-0.231	-0.111	0.380	-0.255	-0.347	-0.570	0.594	1	Total Number	
Female		Time	Locomotion	Rearing	Grooming	Latency	Immobility	Persistent	Acute	Total Time	Total Number		
		Memory	Depression					Pain					

**Significant correlation at the 0.01 level, *Significant correlation at the 0.05

A significant internal correlation was observed among features of depressive behavior in male (r = -0.888) and female (r = -0.946) offspring. Moreover, a significant internal correlation was observed among features of pain behavior in male (r = 0.767, r = -0.886, r = 0.713) and female (r = 0.785) offspring. The red color represents a significant correlation between pain and depression in female (r = 0.767, r = -0.781, r = -0.742) offspring. Moreover, the blue color shows that unlike the control group, avoidance-memory in the female offspring was significantly correlated with depressive-like behavior.

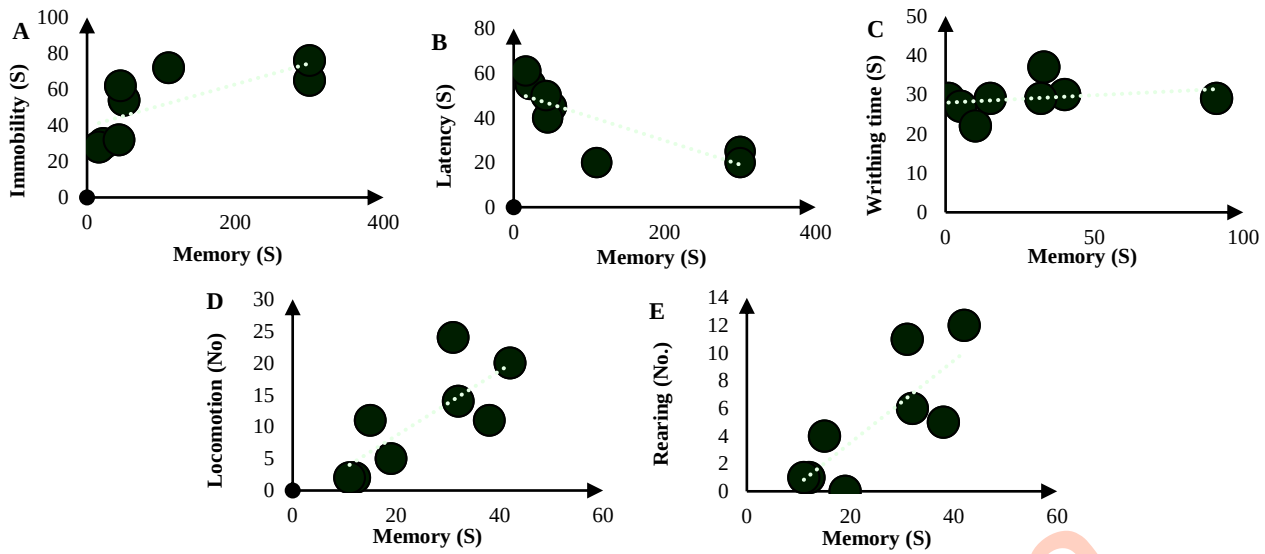

Figure 2. ?????
The figure illustrates a significant correlation among memory and immobility in the female offspring of PMA (A), memory and latency in the female offspring of PMA (B), memory and total time of writhing in the male offspring of MMA (C), memory and locomotion feature of depressive-like behavior in the male offspring of MMA (D) and memory with locomotion in the male offspring of MMA (E).

Morphine Abstinent Parent: The results revealed a significant correlation between pain and depressive-like behavior in the offspring of morphine-abstinent parent(s). However, a significant correlation was only observed in the female offspring of MMA and PMA (Tables 4 and 5).

The results revealed a strong negative correlation between locomotion and total number of writhing episodes in the female offspring of PMA ($R = -0.742$, $P < 0.05$). An increase in locomotion resulted in a decrease in the total number of writhing episodes due to pain behavior (Figure 4, A).

Moreover, in the female offspring of PMA, there was a significant negative correlation between rearing and the total time of writhing ($R = -0.781$, $P < 0.05$). An increase in rearing caused a decrease in the total time of writhing due to pain (Figure 4, B).

Furthermore, there was a significant positive correlation between rearing and acute pain in the female offspring of PMA ($R = 0.767$, $P < 0.05$). An increase in the number of rearing episodes caused an increase in the perception of acute pain in the offspring (Figure 4, C).

Moreover, the results showed a significant correlation between the number of grooming episodes and total number of writhing episodes in the female offspring of MMA (Table 5). The results suggest that with an increase in the number of grooming episodes, the prevalence of writhing in the pain experiment was decreased (Figure 4, D).

Moreover, the results showed that, similar to the offspring in the CTL group, in the offspring of PMA there was no significant correlation between pain and depressive-like behavior (Table 5).

Discussion

The previous study results have signified the important role of maternal inheritance in transgenerational heritage.[10] Other studies have revealed that parental morphine-exposure before gestation elevated morphine preference and anxiety in the first generation of the offspring.[36,37] The results revealed that avoidance memory and pain perception significantly decreased in the offspring of at least one morphine-abstinent parent. Moreover, depressive-like behavior significantly decreased in the female offspring of one morphine-abstinent parent.[10] The effect of parental morphine-exposure on avoidance memory, pain perception, and depressive behavior were summarized in table 1.

Critical analysis of new evidence in medical sciences relies on statistics in terms of correlation.

It is noteworthy that the critical analysis of new evidence needs extensive knowledge of analytic methodologies. Furthermore, correlational analysis has been reported as the most common analytic technique particularly in the epidemiological and health researches.[22,24]

Table 3. Pearson correlation coefficients in the female (left border) and male offspring (right border) of maternal morphine-abstinence

Memory	Time	Memory	Depression					Pain				Male	
		Time	Locomotion	Rearing	Grooming	Latency	Immobility	Persistent	Acute	Total Time	Total Number	Time	Memory
		1	0.769*	0.800*	-0.045	-0.406	0.363	-0.210	0.352	0.111	0.096		
Depression	Locomotion	0.512	1	0.959**	0.251	-0.218	0.116	-0.037	-0.040	-0.075	-0.139	Locomotion	Depression
	Rearing	0.335	0.508	1	0.181	-0.209	0.200	-0.216	-0.010	-0.155	-0.189	Rearing	
	Grooming	-0.236	-0.030	0.266	1	0.381	-0.367	0.756*	-0.310	-0.485	-0.581	Grooming	
	Latency	-0.339	-0.079	-0.029	0.464	1	-0.883**	0.191	-0.120	0.051	0.097	Latency	
	Immobility	0.627	0.140	0.256	-0.397	-0.854**	1	-0.227	0.278	-0.345	-0.336	Immobility	
Pain	Persistent	-0.601	-0.630	-0.256	0.143	-0.418	0.111	1	0.048	-0.271	-0.375	Persistent	Pain
	Acute	-0.356	-0.425	-0.470	-0.152	-0.487	0.240	0.709*	1	0.311	0.339	Acute	
	Total Time	0.911**	0.129	0.135	-0.212	-0.253	0.563	-0.462	-0.270	1	0.983**	Total Time	
	Total Number	0.268	0.134	-0.454	-0.834*	-0.249	0.234	-0.330	0.284	0.231	1	Total Number	
Female		Time Memory	Locomotion	Rearing	Grooming Depression	Latency	Immobility	Persistent	Acute	Total Time Pain	Total Number		

**Significant correlation at the 0.01 level, *Significant correlation at the 0.05

A significant internal correlation was observed among features of depressive behavior in male (r =959) and female (r = -0.854) offspring. Moreover, a significant internal correlation was observed among features of pain behavior in male (r = 0.983) and female (r = 0.709) offspring. The blue color illustrate a significant correlation between memory and pain behavior in female offspring (r = 0.911) and significant correlation between avoidance-memory and depressive behavior in male offspring (r = 769, r = 800). The red color represents a significant correlation between pain and depression in female offspring (r = -0.834). The results showed that unlike the control group avoidance-memory in the male offspring was significantly correlated with depressive-like behavior.

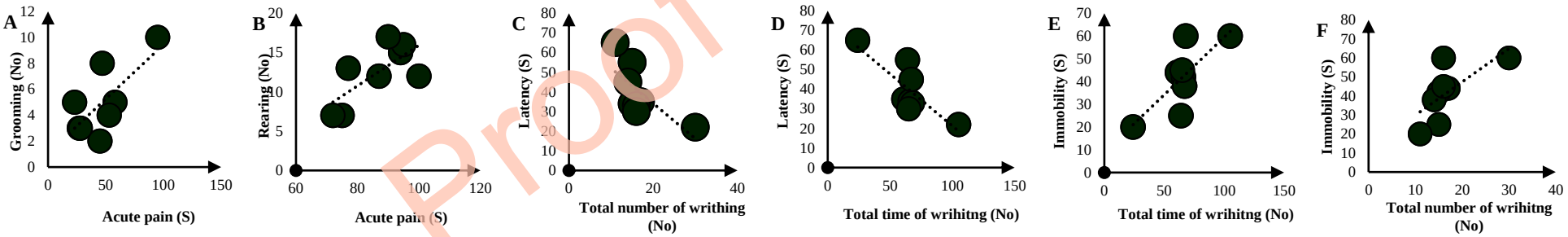

Figure 3. ??????

The figure illustrates a correlation between pain perception and depressive-like behavior in the offspring of healthy parents. It also shows correlation among acute pain and grooming in the female offspring (A), numbers of rearing episodes and acute pain in the male offspring (B), latency and total number of writhing episodes in female offspring (C), latency and total time of writhing in the female offspring (D), immobility and total time of writhing in the female offspring (E), and immobility and the total number of writhing episodes in the female offspring (F). It is noteworthy that, in the male offspring of healthy parents, only the correlation between the number of rearing episodes and acute pain was significant.

Table 4. Pearson correlation-coefficients in the female (left border) and male offspring (right border) of both morphine-abstinence

		Memory	Depression					Pain				Male	
		Time	Locomotion	Rearing	Grooming	Latency	Immobility	Persistent	Acute	Total Time	Total Number		
Memory	Time	1	0.046	-0.254	-0.671	-0.586	0.570	0.057	-0.420	-0.470	-0.526	Time	Memory
Depression	Locomotion	-0.029	1	-	0.364	0.504	-0.662	0.519	-0.490	0.293	-0.192	Locomotion	Depression
	Rearing	-0.113	0.571	1	0.322	-0.051	0.047	0.264	0.071	0.063	0.415	Rearing	
	Grooming	0.442	0.233	-0.023	1	-0.056	-0.234	-0.137	0.458	0.317	0.306	Grooming	
	Latency	-0.130	-0.613	0.154	-0.023	1	-0.878**	0.434	-0.050	0.157	0.092	Latency	
	Immobility	0.335	0.513	-0.301	0.228	-0.927	1	-0.557	-0.040	-0.162	0.082	Immobility	
Pain	Persistent	-0.881	0.296	0.007	-0.369	-0.331	0.114	1	-0.570	-0.314	-0.414	Persistent	Pain
	Acute	-0.587	0.303	-0.007	-0.414	-0.199	0.181	0.620	1	0.575	0.343	Acute	
	Total Time	-0.160	0.540	0.218	-0.589	-0.652	0.420	0.434	0.420	1	0.753*	Total Time	
	Total Number	-0.386	0.787	0.493	-0.069	-0.519	0.233	0.609	0.204	0.662	1	Total Number	
Female		Time Memory	Locomotion	Rearing	Grooming Depression	Latency	Immobility	Persistent	Acute	Total Time Pain	Total Number		

**Significant correlation at the 0.01 level, *Significant correlation at the 0.05

In the male offspring, a significant internal correlation was observed among the features of depressive behavior (r = -0.878) and pain behavior (r = 0.753). No significant correlation was observed between pain and depressive-like behavior.

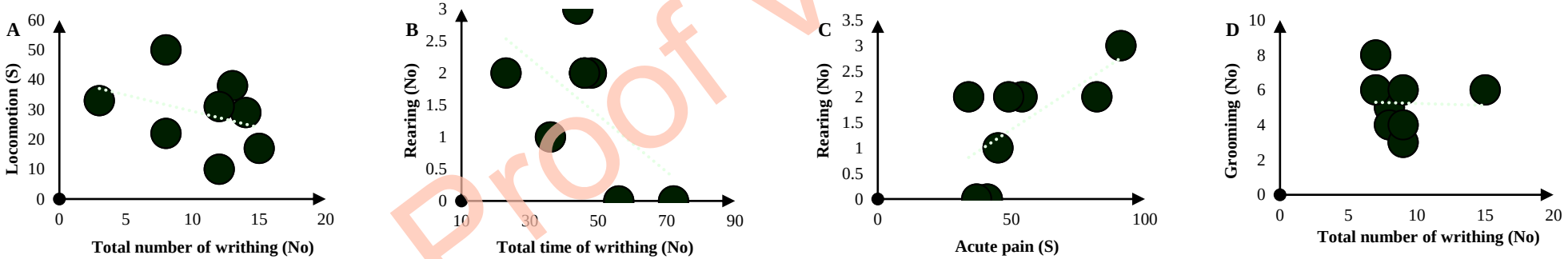

Figure 4. ??????

The figure illustrates the correlation between pain and depressive-like behavior in the offspring of at least one morphine-abstinent parent. It also illustrates correlation among locomotion and total number of writhing episodes in female offspring of PMA (A), rearing and total time of writhing in female offspring of PMA (B), rearing and accumulation in female offspring of PMA (C), and grooming and total number of writhing episodes in the female offspring of MMA (D). It is noteworthy that a strong correlation between pain and depressive-like behavior was observed only in the female offspring of one morphine-abstinent parent.

Correlational analysis can assist medical professionals in their evidence-based practice.[20] Although, emphasis on statistical significance should be considered by either the effect of sample size or clinical meaningfulness of the relationship.[20] Scientific hypotheses stated in terms of correlation and results of correlational studies could lead to testing of evidence under experimental conditions, and consequently, new findings.[21,22]

Avoidance memory: The results of Pearson analysis revealed that, in the male and female offspring of healthy parents or BMA, there was no significant correlation between avoidance-memory and pain behavior or depressive-like behavior. However, in the female offspring of PMA or MMA, a strong correlation was observed between avoidance-memory and depressive-like behavior. Moreover, the strong correlation between avoidance-memory and depressive-like behavior was observed only in the male offspring of MMA.

Using a dependent correlation, Roth et al. showed that memory in childhood is not differentially related to depression and anxiety in adulthood.[38] Moreover, pain produces a systemic distortion of memory similar to that associated with alteration of mood.[41] Furthermore, Crane et al. revealed that negative cognitive bias and depression symptoms should be assessed in those with memory issues.[40] The results of another study revealed that depression influences memory performance and it was indicated that there is an urgent need for appropriate measurement techniques in studies that are associated with neuropsychological disorders.[41] Altogether the evidence suggests the presence of a relationship between depression and anxiety in healthy animals or human subjects.

Neural centers are involved in opioid-dependence sensory pain and memory overlap in the brain.[44] For instance the amygdala, cingulate cortex, and insular cortex are the regions implicated in these pain and memory issues.[44] If the pain persists, the central nervous system may change (neuroplasticity), which can lead to intractable chronic pain.[43] Therefore, neurophysiological changes related to pain, memory, and learning may lead to a maladaptive learning process and perpetuate chronic pain.[44] Nerve fibers in the periphery transmit messages to the spinal cord and brain through the cortical pathways or thalamus. Moreover, reticular formation between the hypothalamus and amygdala shows that there is an association between memory, pain, and emotions.[45] Moreover, the intensity of pain accentuates pain memory by intense pain within pain recall.[46,47] Other studies have shown that fear response by painful stimulus depends on changes that occur in the amygdala that are mediated by endocannabinoid and NMDA receptors.[48-50] Moreover, the anterior cingulate cortex is involved in cognitive functions and emotional processes of pain and fear memories.[51] Therefore, the relationship between memory and pain could be related to the mechanisms that occur in the primary somatosensory cortex, amygdala, and anterior cingulate cortex.[52] Moreover, addiction overlaps with memory formation that involves the plasticity of certain glutamatergic synapses. Furthermore, drug-exposure might induce alterations in gene expression that result in behaviors that persist for a long time after discontinuation of drug use.[53] Furthermore, parental morphine-exposure even before mating impaired memory state and induced tolerance in the rewarding feature of morphine in the male offspring.[4] Moreover, opioid-exposure, even before mating, possibly changes the hormonal background of parents and alters the developmental pattern of progeny.[4] Altogether, the results of the present study showed that there is a significant association between avoidance-memory and depressive-like behavior in the offspring of opioid-dependent parents and the behavior may be acquired through transgenerational inheritance.

Pain and depressive-like behavior: Results of correlation analysis revealed that there is a strong correlation between pain and depressive-like behavior in female and male offspring of healthy parents. However, the pattern of correlation differed and no correlation was observed between pain and depressive-like behavior in the male offspring of MMA or PMA. Furthermore, the pattern in the male and female offspring of BMA totally differed and no correlation was observed between pain and depressive-like behavior.

Chronic pain is a critical factor in the identification of depression and the coexistence of chronic pain and depression tends to intensify the

http://ahj.kmu.ac.ir, 07 October

severity of both disorders.[19] Sheng et al. reported that the association between chronic pain and depression is not clear, which creates a problem in the management of depression induced by chronic pain.[19] Recent cross-sectional studies have revealed that opioid analgesic use is correlated with increased risk of diagnosed depression and noncancer pain.[54-58] The hypothesis that opioid analgesic exposure is the cause of depression has never been studied in human subjects.[59-61] Moreover, findings of the studies by Volkow showed that depression might develop as a neurobiological or epigenetic consequence of chronic opioid exposure in opioid-dependent individuals.[59,61] Depressive-like behavior and persistent pain are closely correlated with the perspective of the brain region and function of the neurological system; consequently, persistent pain may lead to depression.[19] Sadat-Shirazi et al. found that morphine exposure before gestation made offspring vulnerable to morphine, but did not find similar results in methamphetamine abuse.[62] Another study showed that opioid exposure decreased thermal pain sensitivity in the offspring of morphine-addicted parents. Moreover, injection of a non-effective dose of morphine to parental morphine-exposed offspring leads to the reduction pain sensitivity.[66] The results of the current study suggest that there is a significant association between depression and pain behavior in the offspring of opioid-dependent parents and they may acquire behavior through transgenerational inheritance.

Conclusion

Critical analysis of new evidence in medical sciences relies on statistics in terms of correlation. Evidence-based practice is a new skill of medical professionals as they represent the array of research findings. Correlational analysis can assist medical professionals in their evidence-based practice. The results of the current study signified the importance of correlation analysis in medical sciences and suggest that in the offspring of one morphine-abstinent parent the pattern of correlation among avoidance memory, pain, and depressive-like behavior significantly was changed. Morphine exposure might cause alteration in gene expression, which results in inherited changes in the offspring of morphine-abstinent parents. The findings of the study might guide researchers in the development of novel treatments for drug-addicted individuals and their offspring.

Conflict of Interests

The Authors have no conflict of interest.

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همبستگی میان ویژگی‌های رفتاری در نتاج موش‌های صحرایی دارای والدین معتاد به مورفین

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مقاله پژوهشی

چکیده

مقدمه: بسیاری از تحلیل‌های مهم در علوم پزشکی بر اساس اصول آماری مبتنی بر روابط همبستگی می‌باشد. به این منظور، مهم‌ترین هدف از انجام پژوهش حاضر، بررسی ضرایب همبستگی میان ویژگی‌های رفتاری در نتاج حاصل از والدین معتاد به مورفین بود.

روش‌ها: در این مطالعه، نتاج موش‌های صحرایی که والدین آن‌ها در معرض مورفین قرار گرفته بودند، به چهار گروه «با پدر و مادر سالم، با پدر معتاد به مورفین، با مادر معتاد به مورفین و با پدر و مادر هر دو معتاد» تقسیم‌بندی شدند. سپس میزان ادراک درد، رفتارهای شبه افسردگی و حافظه احترازی آن‌ها مورد بررسی قرار گرفت.

یافته‌ها: همبستگی قوی و مثبتی بین درد و رفتارهای شبه افسردگی در نتاج نر و ماده با پدران و مادران معتاد وجود داشت. همچنین، همبستگی معنی‌داری میان حافظه احترازی و ادراک درد و همچنین، بین حافظه احترازی و رفتارهای شبه افسردگی در نتاج نر و ماده دارای پدران و مادران سالم و دارای پدران و مادران معتاد مشاهده نگردید. در نتاج دارای مادران معتاد، همبستگی قوی و معنی‌داری میان حافظه احترازی و رفتارهای شبه افسردگی وجود داشت.

نتیجه‌گیری: نتایج به دست آمده از تحقیق حاضر، حاکی از اهمیت مطالعات هبستگی در رفتارهای پرخطر و اعتیادآور می‌باشد. همچنین، نتایج نشان می‌دهد که الگوی هبستگی میان ویژگی‌های رفتاری در نتاج دارای پدر و یا مادر معتاد تغییر می‌نماید.

واژگان کلیدی: مطالعه همبستگی، مدیریت، اپی‌ژنتیک، رفتار، مورفین

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