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Original Article

The effects of subchronic social and isolation stresses on learning and memory trend in male rats

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Abstract

Introduction: Psychological stresses influence brain functions such as learning and memory. Environmental factors like types and durations of stress affect brain responsiveness. This study investigated the effects of two subchronic social and isolation stresses on learning, memory, adrenal glands weight and corticosterone levels in the hippocampus and frontal cortex.

Methods: Eighteen male rats were randomly allocated into three experimental groups: control, social stress and isolation stress groups. Rats were under stresses for 7 days. Latency of entrance into the dark room was evaluated as brain function, using the passive avoidance test before inducing of electrical shock (as initial latency) and on days 1, 3, 5 and 7 after foot shock. In addition, corticosterone levels were measured in the homogenized hippocampus and frontal cortex.

Results: The latencies of days 1, 3 and 5 were significantly lower in an isolation stress group than the control group. The latency of day 7 significantly decreased in social and isolation stress groups, compared to the control group. The adrenal glands weight showed significant enhancements in social and isolation stress groups, compared to the control group. Although, the weight of the adrenal glands significantly increased in an isolation stress group, compared to the social stress group. There was a significant enhancement in the corticosterone levels in the hippocampus, but not frontal cortex in isolation stress group.

Conclusion: It was concluded that subchronic isolation stress severely deteriorated brain functions (learning and memory) compared to the subchronic social stress. In addition, isolation stress affected corticosterone levels in the hippocampus more than frontal cortex.

Keywords:
Learning and memory;
Social stress;
Isolation stress;
Adrenal glands;
Corticosterone

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Introduction

Learning and memory are essential for survival and maintaining species, in contrast to environmental variables (Chida et al., 2006). The majority of environmental factors, such as psychological stresses are implicated as potential risk factors for memory impairments in recent clinical surveys (Rothman and Mattson, 2010). In addition, many animal studies demonstrated that the learning and memory deficits might cause by different stressors (Klenerova et al., 2002; Radahmadi et al., 2013). Indeed, stress refers to all internal and external changes that lead to impairments in physiological and psychological functions (Radahmadi et al., 2017b; Simoens et al., 2007). Stress is divided into different subsets based on the type of stress and even its

duration (Jaggi et al., 2011; Radahmadi et al., 2017a; Radahmadi et al., 2017b; Ranjbar et al., 2015). According to the type of stress, there are social, isolation, immobility and many other types of stress that each influences the physiological system of the body through different neural circuits (Campos et al., 2013). For instance, cat-induced stress causes memory impairments (Sandi et al., 2005), heat stress caused cognitive disorders (Lee et al., 2015) and restraint stress accelerated memory deficits via oxidative damage, the corticosterone (CORT) levels and other biochemical stress markers in the hippocampus and frontal cortex (Azadbakht et al., 2015; Dastgerdi et al., 2017; Eidelkhani et al., 2015; Huang et al., 2015; Radahmadi et al., 2017b).

On the other hand, based on the stress duration category, a variety of acute, subchronic and chronic stress exists (Bali et al., 2014; Jaggi et al., 2011; Radahmadi et al., 2017a; Ranjbar et al., 2015; Ranjbar et al., 2017). Previous studies indicated that acute stress improved memory (Henckens et al., 2009; Zheng et al., 2008), whereas chronic stress leads to impairment (Radahmadi et al., 2017a; Ranjbar et al., 2015). In addition, subchronic exposure to noise stress impaired memory and cognition with reduction of locomotor activity in open field test (Naqvi et al., 2012). Cognitive deficits also were caused along with chronic mild stress using the novel object recognition test (Papp et al., 2017). Therefore, it seems that stress studies present paradoxical results on brain functions and memory.

On the other hand, in the current study hippocampus (as the main region of memory) and frontal cortex (as other region of memory) were selected for measuring CORT levels, because they are involved in both memory processing and stress pathway (McEwen et al., 2016). In addition, both regions send excitatory projections to the paraventricular nucleus of the hypothalamus for activating hypothalamus-hypophysis adrenal axis in stress (Kinlein and Karatsoreos, 2015). In addition, these regions have abundant CORT receptor (McKlveen et al., 2015; Raineki et al., 2018).

Despite a vast amount of researches about the stress on brain functions, none of the studies directly determined which one of the sub chronic stress types was more harmful on learning and memory. Therefore, the present study was designed to investigate the effects of two subchronic psychological stresses (social and isolation stress) on learning, memory trend, the weight of the adrenal glands (as one of the stress indexes), as well as hippocampal and frontal cortex corticosterone levels in the same laboratory conditions.

Materials and methods

Experimental animals

Experiments were performed on eighteen adult male Wistar rats weighting 200-250 g. The animals were maintained under 12 h light/dark cycles at controlled temperature (22±2°C) and humidity (50±5%) conditions with *ad libitum* access to food and water. All the experiments were performed in accordance with the standards set by the Ethics Committee of Isfahan University of Medical Sciences and the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80–23, 1996 Rev). All behavioral experiments (learning and memory) were carried out between 14:00 and 16:00 pm. Memory function was evaluated by the passive avoidance test at different intervals (1, 3, 5 and 7 days) after foot electrical shock.

Rats were randomly assigned to the following three groups (n=6 in each group): control, social stress and isolation stress groups. Rats were under social and isolation stresses for seven consecutive days. In addition, at the last day of the protocol, the adrenal glands were carefully dissected and immediately weighed (fresh tissue) as a stress index (Radahmadi et al., 2017a; Ranjbar et al., 2017; Ulrich-Lai et al., 2006). In addition, hemi-hippocampus and hemi-frontal cortex were instantly dissected to be kept on dry ice, for evaluation of CORT level (Dastgerdi et al., 2017).

Experimental procedures

Stress paradigm

For induction of social stress, rats were transferred to the new cage with new neighbors for every 24 hours, as one kind of psychological stress (Grippo et al., 2007). In addition, for induction of isolation stress, rats were kept in individual cages without any other neighbors (Grippo et al., 2007; Kalshetti et al., 2015). Since, rats are social creatures, isolation stress is considered as a psychological stress condition (Grippo et al., 2007). Stress was inducted for seven consecutive days, as subchronic stress and/or mid

stress (7 days) was the strongest stress condition, with respect to other timing of stress (Forsberg et al., 2015; Patki et al., 2013; Ranjbar et al., 2015; Ranjbar et al., 2016; Ranjbar et al., 2017; Sahin et al., 2015).

Behavioral paradigms

The passive avoidance apparatus (64 cm × 25 cm × 35 cm) divided into two compartments of identical size (32 cm × 25 cm × 35 cm) with sliding guillotine doors and grid floors. On the first day, rats were placed in the light compartment and were allowed to explore the whole apparatus (sliding door open) without the electrical shock over a period of 300s. The day after, an acquisition trial was performed, rats were placed individually in the light compartment for the 60s and then the sliding door was raised. When the rat entered the dark compartment, the door was closed and an inescapable scrambled single foot electric shock (0.5mA, 2s; once) was delivered through the grid floor by a shock unit (Dastgerdi et al., 2017). The initial latency of entrance into the dark room was recorded before inducing of electrical shock. In probe trials (1, 3, 5 and 7 days after foot shock), the rat placed in the light compartment again for 60s, then the sliding door was raised and rat accessed to the dark compartment without any shock. The time to enter the dark compartment (up to a maximum of 300s) was recorded. If an animal did not enter the dark compartment within 300s, the trial was terminated. The absence of entry to the dark compartment or a longer duration in the light compartment indicated as a positive response, because the passive avoidance task determines the ability of a rat to remember a foot shock delivered. In addition, latencies of the initial and probe trial on day 1 (before and after foot shock, respectively) indicated learning. Meanwhile, memory changes have been shown by the comparison of probe trial latencies (Hosseini et al., 2014; Radahmadi et al., 2013; Radahmadi et al., 2015a).

Measurement of adrenal glands weight

At the end of the experimental period, adrenal glands weight were measured for each rat.

Assessment of CORT levels in the hippocampus and frontal cortex

At the end of the experiments, the animals were sacrificed at 12:00–14:00 pm by decapitation on day 8. Following decapitation, the brain of each animal was immediately dissected from the skull and the hemi hippocampus and hemi frontal cortex were instantly dissected to be kept on dry ice, which were subsequently immersed in Problock™ 50, EDTA free (Gold Bio Co., USA) and in a phosphate buffer solution (0.01M, pH 7.4), separately. Indeed, this solution contained a complete protease inhibitor cocktail (Radahmadi et al., 2015a). The hippocampus and frontal cortex were homogenized and centrifuged in a cooled centrifuge (4°C, 10,000g) for 20 min. The supernatant was collected and stored at −80 °C, until further assessment. The commercial Enzyme Linked Immuno Sorbent Assay (ELISA) kit (Zellbio Co., Marburg, Germany) was used to assess the CORT level in the hippocampus and frontal cortex. The amount of CORT was determined in a given volume of the supernatant (Dastgerdi et al., 2017; Radahmadi et al., 2015a; Radahmadi et al., 2015b).

Statistical analysis

Biochemical and behavioral data on days 1, 3, 5 and 7 were analyzed using the one-way ANOVA followed by LSD post-hoc test for multiple comparisons. Also, the differences of memory trend were analyzed, using the repeated measures ANOVA followed by LSD post-hoc and intragroup differences, such as a comparison between initial and latency 1 day (before and after electrical shock, respectively in each group) was analyzed, using the paired t-test. All the data were reported as means±SEM. The *P* value of less than 0.05 ($P<0.05$) was declared significant.

Results

Latency time of passive avoidance

Based on the one-way ANOVA test, no significant differences were observed in initial latency in all experimental groups (Fig. 1A). Meanwhile, one-way ANOVA test showed significant differences in the latencies of day 1 ($F[2,16]=3.775$, $P<0.05$), day 3 [$F(2,16)=6.063$, $P<0.01$], day 5 ($F[2,16]=4.176$, $P<0.05$) and day 7 ($F[2,16]=24.452$, $P<0.001$).

In the isolation stress group, the latencies of day 1, 3 and 5 were significantly ($P<0.05$, $P<0.01$ and $P<0.01$, respectively) lower than similar trials of the control group (Fig. 1B-D). In addition, latency of day 3 significantly ($P<0.05$) decreased in an isolation stress group, compared to the social stress group (Fig. 1C).

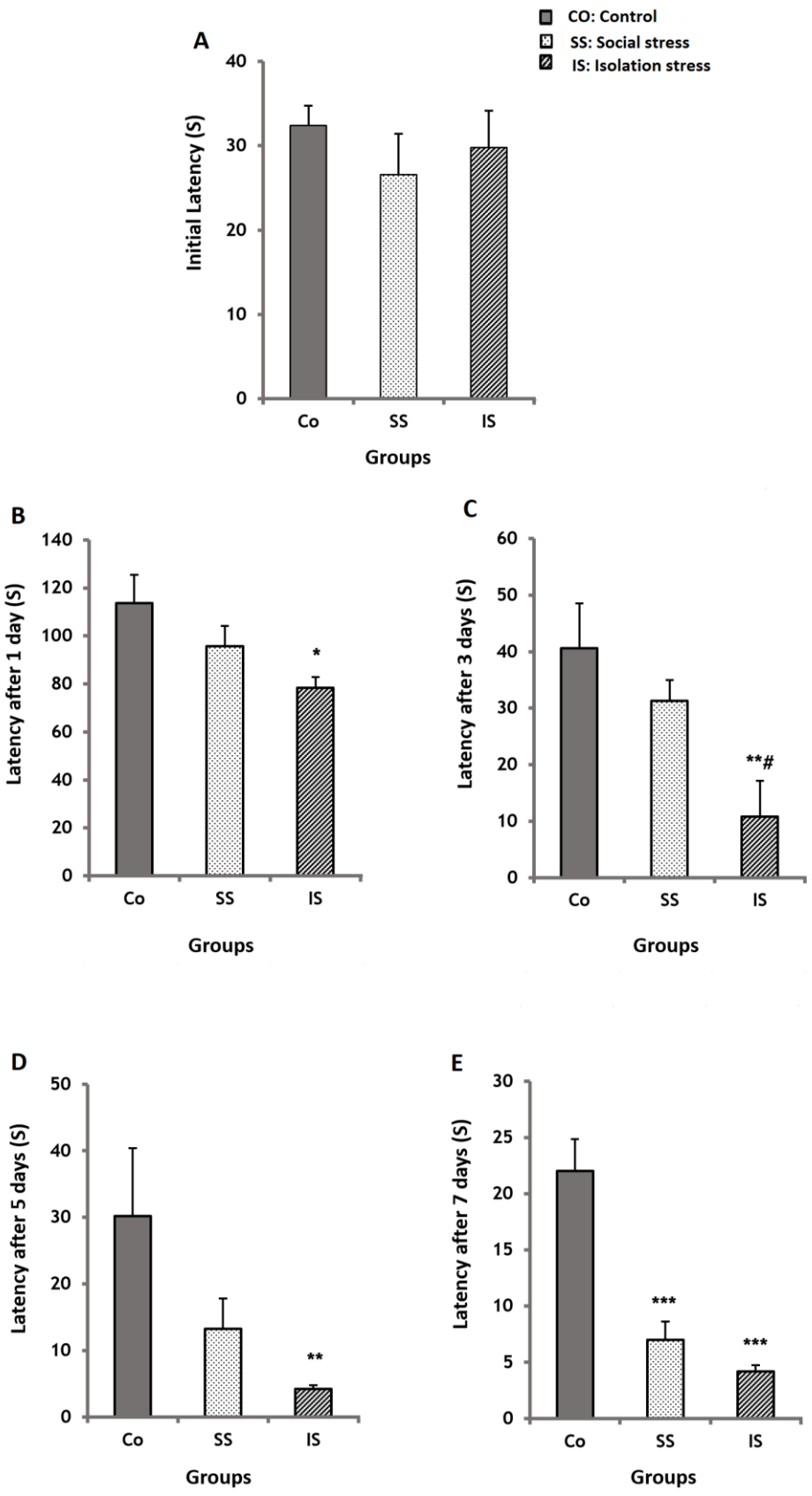

Fig.1. A) Initial latency to enter the dark compartment of the passive avoidance apparatus for all groups, before receiving the foot shock. B, C, D and E) The latency to enter the dark compartment of the passive avoidance apparatus for all groups on days 1, 3, 5 and 7 respectively, after receiving the foot shock. Data are presented, using one-way ANOVA statistical analysis followed by LSD post-hoc test. Results are presented as mean±SEM. There was no significant difference between all groups. *P<0.05, **P<0.01 and ***P<0.001, compared to the control group and $^{\#}$ P<0.05 compared to the social stress group.

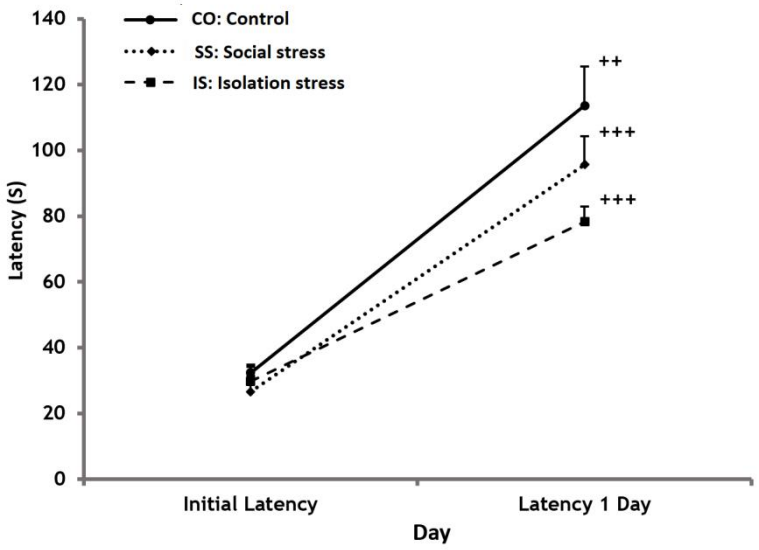

Fig.2. Initial latency and the latency, one day after receiving a foot shock to enter the dark compartment of the passive avoidance apparatus, before and after receiving a foot shock within groups. Results are presented as mean±SEM, using Paired sample t test. ^{++}P<0.01 and ^{+++}P<0.001: latency 1 day, compared to the initial latency.

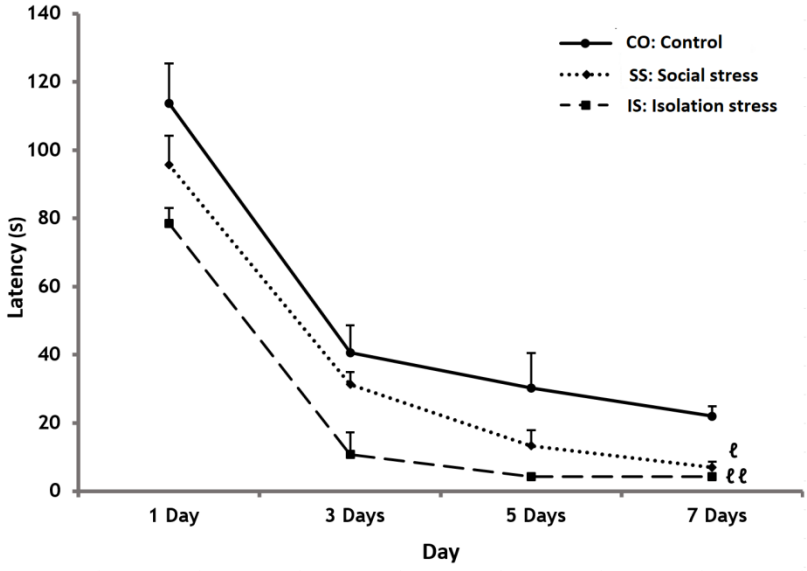

Fig.3. Trend line of latency, after electrical foot shock delivery (within groups). Results are presented as mean±SEM, using repeated measure one-way ANOVA, followed by LSD post-hoc test. ^{ℓ}P<0.05 and ^{ℓℓ}P<0.01, compared to the control group.

It indicated the destructive effects of subchronic isolation stress with respect to social stress. In social and isolation stress groups, the latency of day 7 showed significant (P<0.001 in both of them) decreases, compared to the control group (Fig. 1E).

Based on the paired t-test, the data revealed that there were upward significant (P<0.01 in control group and P<0.001 in both stress groups) differences between initial latency and latency 1 day in all three groups (Fig. 2). In general, learning happened in all experimental groups, as learning was lower in stress groups, particularly in an isolation stress group.

As shown in figure 3, the trend lines of latencies in four trials (1, 3, 5 and 7 days after the foot shock) were downward in all experimental groups. Based on the repeated measure ANOVA test, the memory trend line showed significant (P<0.05 and P<0.01) decreases in social and isolation stress groups, respectively, compared to the control group.

Assessment of adrenal glands weight

Based on the one-way ANOVA test, there was a significant (F[2,16]=9.545, P<0.01) difference in the weight of the adrenal glands. In addition, the weight of the adrenal glands in social and isolation stress groups had significant (P<0.05 and P<0.01, respectively) enhancement, compared to the control group. Also, adrenal glands weight had a significant

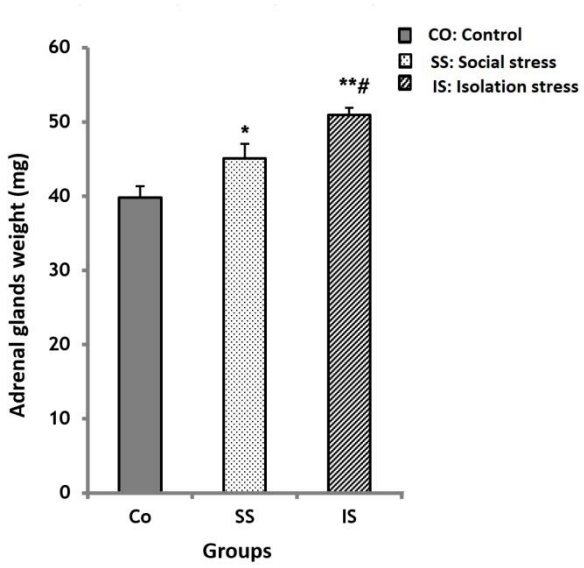

Fig.4. The comparison of the weight of the adrenal glands in the experimental groups. Data are presented, using one-way ANOVA statistical analysis, followed by LSD post-hoc test. Results are presented as mean±SEM. *P<0.05 and **P<0.01 compared to the control group. $^{\#}P$<0.05 compared to the social stress group.

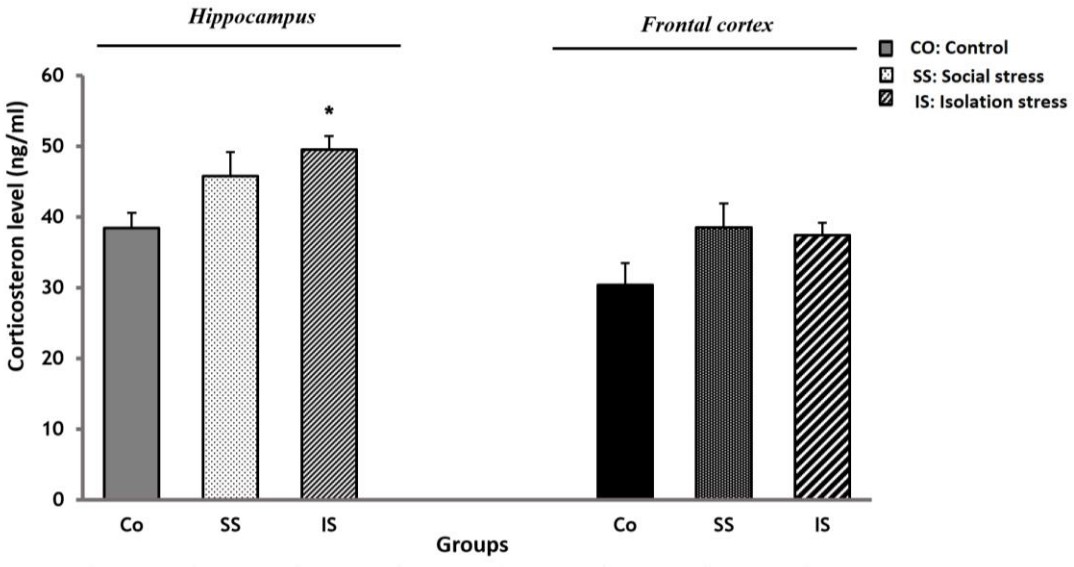

Fig.5. The comparison of the weight of the adrenal glands in the experimental groups. Data are presented, using one-way ANOVA statistical analysis, followed by LSD post-hoc test. Results are presented as mean±SEM. *P<0.05 and **P<0.01 compared to the control group. $^{\#}P$<0.05 compared to the social stress group.

(P<0.05) enhancement in isolation stress group compared to social stress group (Fig. 4). In addition, the increase in left adrenal weight was more than right adrenal (graph not presented).

Assessment of CORT levels in the hippocampus and frontal cortex

Based on the one-way ANOVA test, there was a significant (F(2,16)=3.897) difference in hippocampal CORT levels. As shown in figure 5, there was a significant (P<0.05) enhancement in the CORT level in the hippocampus, but not the frontal cortex in the subchronic isolation stress group, compared to the control group; however, in the subchronic social stress group, there were no significant CORT levels differences in the hippocampus and the frontal cortex (Fig. 5).

Discussion

The effects of two subchronic psychological stresses (social and isolation stress) were investigated on

learning and memory trend, in order to determine which one of stress types (social and isolation stress) is more destructive on learning and memory. Present study showed that both subchronic stresses led to changes on learning. Indeed, learning decreased in both subchronic social and isolation stress conditions (Fig. 2). Frisone et al. (2002) reported the chronic isolation stress deteriorated the spatial learning on the Morris water maze. In addition, the chronic restraint stress impaired learning through the passive avoidance test (Dastgerdi et al., 2017; Radahmadi et al., 2013). Therefore, based on previous and present studies, it seems that different types of stress decreased learning as one of brain functions.

Both types of stress (social and isolation stresses) affected memory on the first day, as shown in the figures 1 and 3. Although, memory significantly impaired in an isolation stress group after 1 day (Fig. 1B), whereas, memory deficit significantly happened after 7 days in the social stress group (Fig. 1E). Some previous studies reported that social stress also impaired memory (Duque et al., 2016; Duque et al., 2017; Garcia-Pardo et al., 2017). In contrast, Monleón et al. (2015) reported even ten-minute encountering to social stress deteriorate the memory; however, in the current study, memory was impaired in an isolation stress group earlier than social stress group (Fig 1). It is possible that emotional state is more in the social stress than the isolation stress. In addition, some studies indicated that adrenaline enhanced memory on 1 day stress (acute stress) (Goldfarb et al., 2017). Therefore, it seems that perhaps, adrenalin was released from the adrenal glands at first day of social stress that can nearly protect memory in the social stress. In this way, some studies reported that isolation stress eliminates the social behaviors of rats (Chida et al., 2006; Manni et al., 2009). Also, the isolation stress may lead to depression-like behavior and depletion of serotonin and norepinephrine (Brenes et al., 2008; Hayley et al., 2005). Hence, caused pathophysiological changes, such as decreased learning abilities (Chida et al., 2006; Manni et al., 2009). Different mechanisms may involve in memory impairments in isolation stress such as elevated serum CORT level (Chida et al., 2006), the alternations of the dopaminergic system (Dalesman and Lukowiak, 2011; Del Arco et al., 2004) and morphological changes in the brain (Bianchi et al., 2006; Pittenger and Duman, 2008). Pittenger and Duman (2008) reported that eight weeks of isolation stress decreased the dendritic spines in the medial prefrontal cortex that are important for attentional behavioral tasks. Furthermore, Bianchi et al. indicated the decreased expression of the synaptic protein, newborn neurons, dendritic length and dendritic spine density of pyramidal cells happen in the hippocampus along different durations of isolation stress (Bianchi et al., 2006). Moreover, it seems that both of neurophysiological and anatomical changes attenuate the brain functions, such as memory due to isolation stress. In addition, the CORT levels in the hippocampus and frontal cortex nearly confirmed the impairment of memory in subchronic isolation stress, with respect to social stress condition; however, the changes of CORT levels were more in the hippocampus than frontal cortex (Fig. 5). Furthermore, it confirmed that, hippocampus (as the main region of memory) played a fundamental role in stress condition with respect to frontal cortex (as other region of memory). Miachon et al. (1993) reported that the thirteen-weeks of isolations stress changed the CORT releasing in hippocampus, cortex and cerebellum. Furthermore, some human studies demonstrated cognitive deficits are drastically related to CORT level and hippocampus function (Hinkelmann et al., 2009; Kamal et al., 2014). In the present study, increased hippocampal CORT levels confirmed memory deficit in an isolation stress condition. It seems that memory impairments may be related to CORT level.

In the present study, memory trend also decreased in the subchronic social stress and particularly isolation stress group, compared to the control group (Fig. 3). Some researchers have shown that stress had harmful, beneficial and no effects on neural health and brain functions (Radahmadi et al., 2013; Radahmadi et al., 2006). Therefore, it seems that stress had paradoxical effects on memory processing. For example, Schwabe and Wolf (2013) introduced stress as a critical factor for optimizing learning and memory, while some studies indicated that the chronic stress caused the hippocampal pathology and impaired the memory function (Radahmadi et al., 2016; Radahmadi et al., 2014; Rothman and Mattson, 2010). In this way, previous studies demonstrated that different durations of stress had different effects on brain functions

(Radahmadi et al., 2017a; Ranjbar et al., 2015). Since, in the present study, the stress duration was the same in both stress groups, it seems that, the type of stress affected trend of memory. Based on the current study, it is proposed that subchronic isolation stress deteriorated memory trend severely in the passive avoidance test with respect to social stress. Therefore, it seems that social and isolation stresses disrupted the normal functions of learning and memory using the different neural mechanisms in the same duration of stress.

Other current findings showed the increased adrenal glands weight (as a stress index) in both stressed groups, particularly in an isolation stress group (Fig. 4). Parallel to these findings, studies indicated that chronic social stress caused the enlargement of the adrenal glands (Czeh et al., 2007; Rygula et al., 2005; Schmidt et al., 2007). A study demonstrated isolation stress led to depression-like symptoms (Kokare et al., 2010). Furthermore, the depressed behavior increased the CORT plasma level and the weight of the adrenal glands in human studies (Nemeroff et al., 1992; Ulrich-Lai et al., 2006).

Conclusion

To sum up, type of subchronic psychological stress was an effective factor on hormonal and behavioral changes related to hippocampus. In other words, isolation stress impaired the learning and memory trend more than social stress. Furthermore, significant elevation of the CORT level in hippocampus indicated the important role of this structure in an isolation stress condition. Therefore, it seems that subchronic isolation stress was more destructive than social stress on brain functions; however, further studies are required to shed more lights on the possible mechanism(s) involved in memory and learning alternations to stress conditions. In addition, the assessments of biochemical factors such as neurotransmitters and other stress hormones in hippocampus may be more appropriate to determine the mechanism(s) of different kinds of stress on brain functions.

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Conflict of interest

There are no conflicts of interest that have been reported by the authors or by any individuals in control of the content of this article.

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