

Music Alleviates Learning and Memory Impairments in an Animal Model of Post-Traumatic Stress Disorder

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Abstract: Post-traumatic stress disorder (PTSD) is the most prevalent disorder that occurs after experiencing life-threatening traumatic or stressful events. The most prevalent problems among PTSD patients are cognitive dysfunctions, including learning and memory impairments. Listening to music has constructive effects on brain functions, neurogenesis, and neuroplasticity, so the aim of the present study was to investigate the effect of music on learning and memory in a rat model of PTSD. Fifty-six adult male Wistar rats (200–250 gr) divided into four main groups (control, music, PTSD, and PTSD+ music) were used. A single prolonged stress (SPS) method was used for inducing PTSD in rats. Anxiety-like behaviors and Cognitive functions were evaluated using the Open field, Morris water maze (MWM), and passive avoidance test. Findings demonstrated that SPS induced marked impairment in learning and memory, and anxiolytic behaviors in rats and exposure to music significantly ameliorated these impairments. It seems that music can modulate the destructive effects of SPS on learning and memory at a behavioral level.

Keywords: PTSD; Music; Learning and memory; Anxiety-like behavior; rat.

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1. Introduction

Post-traumatic stress disorder (PTSD) is one of the main psychiatric disorders with a lifespan prevalence of 5–8% in the general population [1]. PTSD occurs when a person is exposed to a life-threatening traumatic or stressful events [2].group of symptoms for PTSD includes an intrusion, avoidance, negative alterations in cognition, mood, alterations in arousal and reactivity[3]. Hippocampus, Amygdala, and Medial Prefrontal Cortex are the brain regions involved in the pathophysiology of PTSD[4].one of the most common problems among these patients is cognitive dysfunctions [5]. Amygdala and hippocampus play an important role in learning and memory ability. Memory is an important process enabling humans to survive through learned adaptive behaviors [6]. An animal model of PTSD is similar to various neurodegenerative diseases [5]. Single-prolonged stress (SPS) is frequently used as an animal model for PTSD. This rat model of PTSD was described by liberzon 22 years ago [7]. Studies have shown a reduction in the volume of the hippocampus and amygdala of people suffering from PTSD. [8]. PTSD animal models also resulted in impairments in learning and memory [9-13]. A number of therapies like Eye Movement Desensitization and Reprocessing Therapy [14], Cognitive Processing Therapy [15], Prolong Exposure [16], and Trauma-Focused Cognitive Behavioral therapies [17] are applied for helping and treating patients with PTSD.

Music, as a non-pharmacological treatment tool has the potential to cure clinical and functional symptoms in individuals struggling with post-traumatic stress [18]. Many researches revealed that therapy with music diminishes stress and anxiety in clinical populations [19-22]. Also, studies have demonstrated that music can reduce emotional distress [23-25], foster social connectedness [26], and improve overall wellbeing [27]. The previous finding showed that listening to music stimulates many regions of the brain from the brainstem to the frontal cortex [28]. The music stimulates the hippocampus, amygdala, nucleus accumbens, and mesolimbic dopaminergic system [29], which also has profound beneficial effects on brain functions, neurogenesis, and neuroplasticity [30,31]. Spatial cognition is improved in developing rats after Music exposure [32]. During the developmental period of the auditory cortex in growing rats, Mozart music could enhance spatial learning and memory [33,34]. Also, it has been shown that classical music significantly improved learning and memory among stress-induced rats [35]. Considering the protective effects of music on learning and memory impairments, it appeared that music has beneficial effects on PTSD-induced cognitive impairments. Therefore, in the present effects of music exposure on anxiety-liked behavior, spatial and passive avoidance learning and memory in an animal model of PTSD were studied.

2. Materials and Methods

Fifty-six healthy male Wistar rats (200–250 gr) were used to develop an animal model of PTSD. Animals were kept in accordance with animal care guidelines of Kerman University of Medical Sciences, Kerman, Iran (23 ± 1 °C, 12 h light/dark cycles and ad-libitum access to food and water). A maximum effort was made to minimize pain and discomfort for the animals. This study was approved by the Kerman Neuroscience Research Center (Ethics code: 97-23). Rats were randomly divided into four main groups (14 rats for each group): control, PTSD, music (mu), PTSD+Music (ptsd.mu), and each group contained two subgroups: seven rats for Open field and Morris water maze tests and seven rats for Shuttle box test. All behavioral experiments were conducted between 9:00 AM and 2:00 PM.

To induce PTSD in animals, the Single Prolong Stress (SPS) procedure was used as one of the most common models proposed by Liberzon et al. in 1997 [7]. According to this method, SPS is conducted in three stages. First, rats were restrained for 2hr by placing inside a polyethylene restrainer. Second, instantly afterward, 20 minutes forced swim was performed in a cylindrical tank (with 40 cm diameter, 50 cm height, and filled two-thirds from the bottom with 24°C water). Third, following recuperation for 15 min, they were exposed to diethyl ether (Sigma-USA) until the loss of consciousness and then left undisturbed in their home cages. Seven days after PTSD, rats were again brought to the laboratory and were undergone all behavioral tests after one-hour of habituation.

Rats in music groups were exposed to 12 h daily Mozart's piano sonata K.448 music for seven days, starting from 7:00 to 17:00. Mozart K.448 was usually used in studies that produce a musical effect on the brain of rodents [36-38].

Arena made of Plexiglas (90 × 90 × 45) cm was used for the Open field test. The apparatus floor was divided into 16 squares, so the field was divided into central and peripheral squares. To check spontaneous locomotor activity, anxiety, fear-related behavior, including total distance moved in cm (TDM), a number of grooming and rearing, time spent in periphery and center, the animal was placed in the center of the arena, and their behavior was recorded for 5 min with Ethovision video-tracking system [39].

MWM was performed to evaluate related hippocampal learning and memory. Rat uses spatial clues while swimming to locate a submerged platform. The test chamber was a circular pool (160 cm diameter and 60 cm deep), which was filled with water (35 cm depth and $25 \pm 0.5^\circ\text{C}$) and surrounded by visual cues visible to animals. A circular submerged platform (15 cm wide and 35 cm height) was placed 1.5 cm below the water surface at a fixed location in the center of one of the four imaginary quadrants. In the learning phase, three blocks were fulfilled, and each block has four trials. During each trial, animals were inadvertently released into one of the quadrants and permitted to swim for 60 s to probe concealed platform. The location of the platform did not change during the acquisition trials, and each rat was allowed to swim for 60 s to find the platform. After the locating platform, each animal was allowed to remain there for 20–30 s and then returned to its cage to wait for 20–30 s before the start of the next trial. The time and distance traveled to find the escape platform was recorded in each trial. A single probe trial was performed 2 h after the last block to test spatial short term memory retention. In this trial, the platform was removed, and animals were allowed to swim freely for 60 s. The distance and time spent in the target quadrant were collected for each rat to measure spatial memory. Behavioral data for MWM was collected using Ethovision automation software (Noldus Ethovision® system, version 7, Netherland), rats could be traced on the screen of a computer [39]. All experiments were carried out between 9:00 AM and 2:00 PM.

In Passive avoidance test (PAT) rats learned to avoid an environment in which a prior aversive stimulus has been delivered. The apparatus consisted of two compartments (dark and light) of the same size ($20 \times 20 \times 30 \text{ cm}^3$) separated by a door that could be lifted manually. This test had two phases: learning and memory. The rats were allowed to habituate in the experimental room for at least 30 min before experiments. Then, each animal was gently placed in a brightly lit compartment of apparatus; after 5 s the door was opened, and the animal was allowed to enter the dark module. The latency with which animals entered the dark chamber was recorded. Animals that waited for more than 120 s to enter the dark chamber were excluded from experiments. Finally, one hour after previous exposure to the apparatus, the animal was placed into a light compartment, the door was opened, and, on entering the dark compartment, it was given an electric shock (0.5 ma, 2 ms; via wires embedded in dark chamber floor). This phase was repeated up to five times at a 1-hour interval until the animal learned to avoid dark compartment (remains in the light compartment for at least 300 s), and the number of shocks required for learning was recorded. The memory phase of the test was performed 2 hours after the learning phase. The animal was placed in a light chamber (door closed), and, after 5 s, the door was opened, and the time taken by the animal to enter the dark chamber was recorded as Step-Through Latency (STL). The total time spent in the Dark Compartment (TDC) over a duration of 5 minutes after the door opening was also recorded[40]. After each trial, the apparatus was cleaned using 70% alcohol.

The data were averaged and offered as Mean \pm SEM. The effect of music on spatial learning rates among different groups in MWM was evaluated by repeated measure two-way ANOVA followed by a Tukey's post hoc test. Data obtained in MWM probe trials, open field, and passive avoidance test were analyzed by a one-way ANOVA. All post-hoc comparisons were made using Tukey's post-hoc test. A P value of less than 0.05 was considered statistically significant. All statistical analyses were done using SPSS software (version 22.0).

3. Results and Discussion

3.1. Effect of PTSD and music on locomotion and anxiety-like behaviors in an open field test.

As shown in an open field test, time spent in inner zone (Fig. 1-A) and frequency of rearing (Fig. 1-C) and grooming (Fig. 1-D) in PTSD group were significantly altered ($P < 0.01$, $P < 0.001$ and $P < 0.05$ respectively) compared to control group which indicated PTSD could disturb these anxiety-liked behaviors. The number of rearing behavior and time spent in the inner zone was significantly ($P < 0.01$ and $P < 0.05$ respectively) changed in PTSD+ Music group (ptsd.mu) compared to PTSD group (PTSD), which revealed music could improve these anxiety-liked behaviors. There is no significant difference between all groups in the total distance, which implies that there is no impaired motor function (Fig. 1-B).

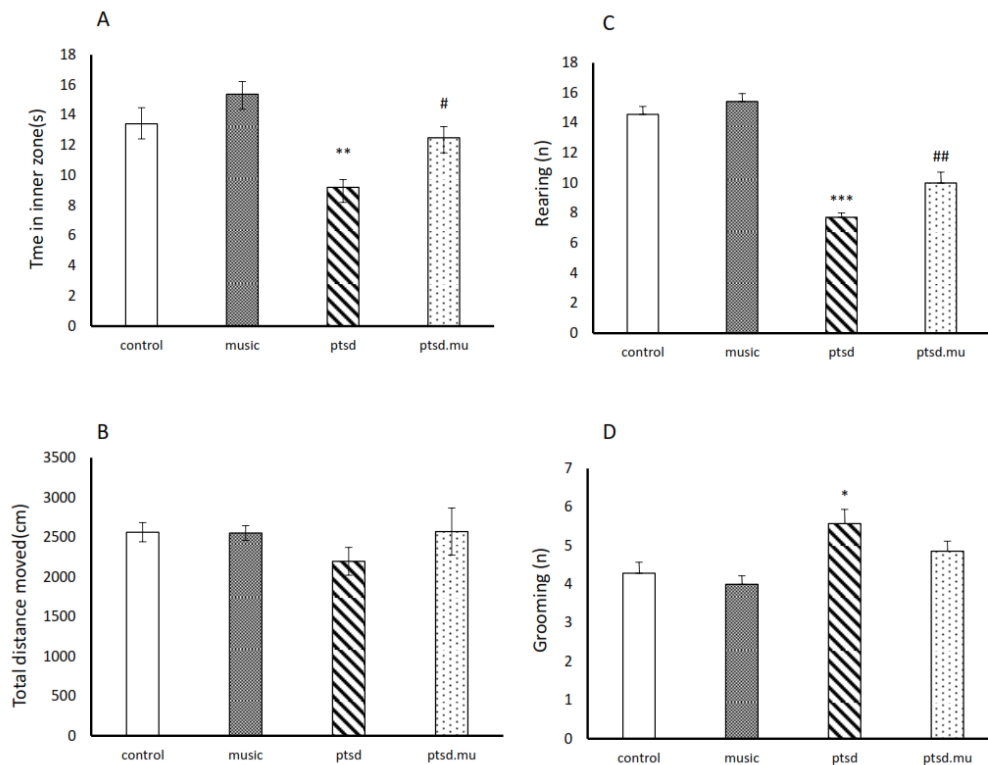


Figure 1. The effect of PTSD and music on locomotion and anxiety-like behaviors using with open field test. * $P < 0.05$, ** $p < 0.01$ and *** $p < 0.001$ in comparison to the control groups and # $p < 0.05$, ## $p < 0.01$ in comparison to ptsd group.

3.2. Effect of PTSD and music on learning and memory in the Morris water maze test (MWM).

Reducing in the escape latency and swimming path length to explore the hidden platform in MWM during training blocks was acknowledged as spatial learning. Two-way ANOVA revealed that there were statistically significant differences in escape latency ($p < 0.05$ in block 1 and 2 and $p < 0.001$ in block 3) and path length ($p < 0.05$ in block 1, $p < 0.01$ in block 2 and $p < 0.001$ in block 3) to explore the hidden platform in PTSD group compared to control group, showing spatial learning impairment in PTSD rats. Also, as shown, scape latency and path length were significantly ($p < 0.001$ and $p < 0.01$ respectively) diminished in PTSD.mu group as compared to PTSD group in block 3. It seems music could improve spatial learning in PTSD rats (Fig. 2 A-B).

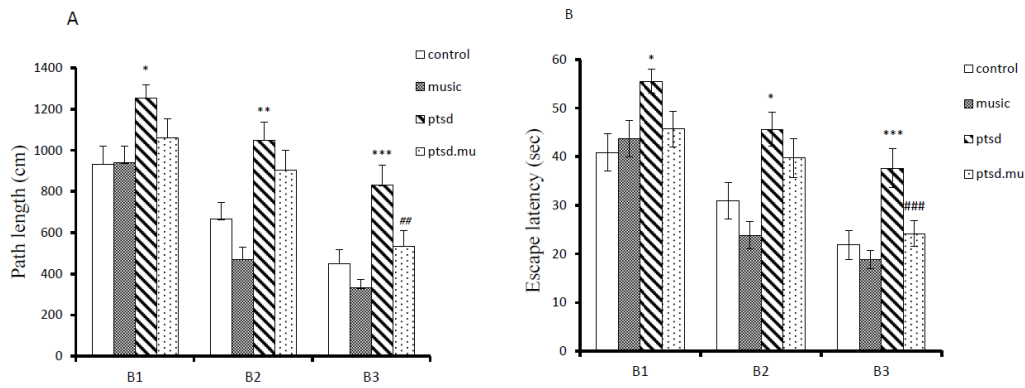


Figure 2. The effect of PTSD and music on spatial learning in MWM task. * $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$ in comparison to the control groups and ## $p < 0.01$, ### $p < 0.001$ in comparison to ptsd group.

Two hours after the training phase (acquisition phase), short-term memory retention was tested. The mean percentage (%) for time and distance in the target quadrant was analyzed data for the retention test. By one-way ANOVA indicated that these parameters were decreased in PTSD group compared to the control group ($p < 0.05$). It showed that PTSD could disturb spatial memory. There was no statistically significant difference between PTSD group and PTSD.mu group. Therefore music did not affect spatial memory in PTSD rats (Fig. 3 A-B).

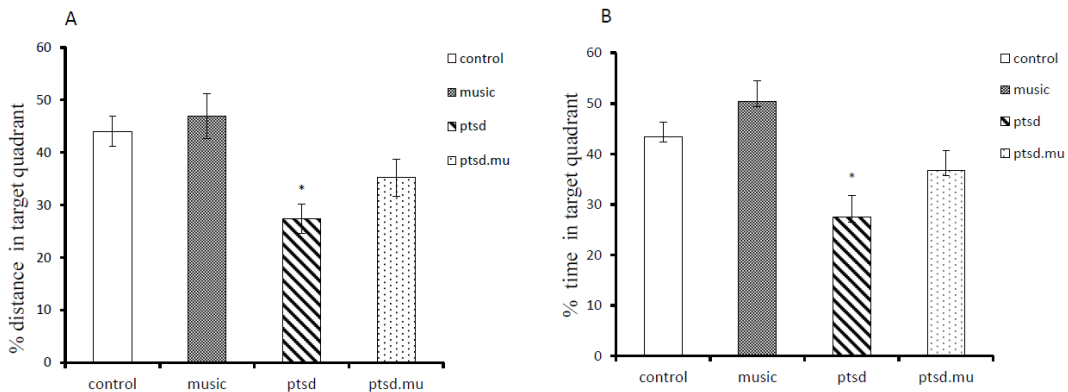


Figure 3. The effect of PTSD and music on spatial memory in MWM task. * $p < 0.05$ in comparison to the control.

3.3. Effect of PTSD and music on learning and memory in passive avoidance test (Shuttle Box).

The influence of PTSD and music on passive avoidance learning is shown in Fig. 4-A. One-way ANOVA results indicated that the number of shocks received by animals of PTSD group was significantly higher than those of the control group during the training session ($P < 0.05$). This indicates learning impairment in PTSD animals. Exposing ptsd.mu group to music decreased the number of shocks in comparison to PTSD group ($P < 0.05$). It showed that music could improve PTSD-induced learning impairment. The short term memory retrieval was performed 2 h following a training session and step-through latency (STL). Time spent in a dark compartment (TDC) was analyzed to evaluate short term memory retrieval. The TDC and STL were also altered in PTSD group in comparison with control groups ($P < 0.001$). This clearly revealed memory impairment in these animals. Our findings indicated that exposing PTSD rats to music in ptsd.mu group ameliorated their memory deficit ($P < 0.05$) compared to PTSD group (Fig. 4 B-C).

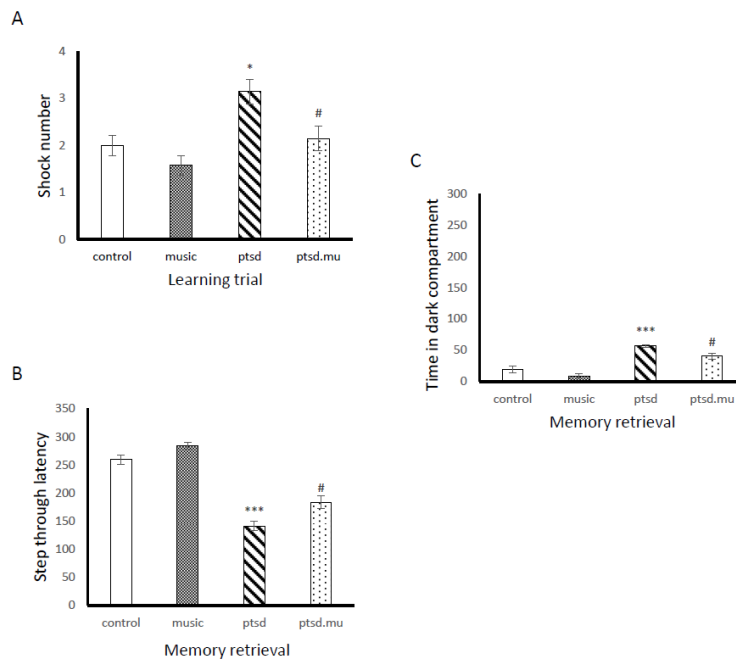


Figure 4. The effect of PTSD and music on passive avoidance learning and memory in the Shuttle box test. * $p < 0.05$, and *** $p < 0.001$ in comparison to the control groups and # $p < 0.05$ in comparison to PTSD group.

3.4. Discussion.

Influence of PTSD induced by SPS on anxiety-like behaviors, spatial, and passive avoidance learning and memory was analyzed, and then the effects of music on impairment in cognitive behaviors induced by PTSD were also studied. Principal findings of this study are that (I) PTSD induced marked impairment of learning and memory and anxiolytic behaviors in rats; (II) exposure to music significantly improved and ameliorated these impairments.

PTSD, as a debilitating condition, significantly declines the quality of life in patients[41]. PTSD-induced animals show severe degenerative alterations and neuronal cell loss in the autonomic nervous and sensory system[42-45]. Excessive stress is known to cause a deteriorative effect on cognition and memory in humans and animal models[46,47].

Our results are consistent with Masoumi-Ardakani et al. (2017) results, which demonstrated that SPS caused anxiolytic behaviors in rats[48]. Also, previous studies have shown that SPS produced spatial memory impairments in Morris water maze [49-51]. Elizalde et al. (2008) revealed that chronic mild stress induces recognition memory deficits in mice [52]. Another study indicated that social isolated stress impaired passive avoidance learning and memory[53], in this study it is revealed that SPS procedure could also induce these types of impairments

Over the past decades, numerous studies have focused on identifying the pathophysiology of PTSD. It has been suggested that structural brain abnormalities associated with PTSD mainly involve the amygdala, hippocampus, and medial prefrontal cortex[54]. The hippocampus, in particular, is thought to be involved because of its critical role in learning and memory, as well as its regulation of the hypothalamic-pituitary-adrenocortical axis[55]. Since dendrite atrophy and neuronal cell death occurs in PTSD and chronic stress exposure, memory impairment, and behavioral malfunctions are seen [56].

To our knowledge, this research is first showing the effect of music in PTSD animal model. The results showed that music alleviated anxiety-like behaviors, spatial learning, and passive avoidance learning and memory impairments induced by PTSD.

Several drugs, like selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors (SNRI) have been proposed to prevent and treat symptoms of PTSD. [57]. Although they have positive effects on PTSD symptoms, their use is restricted because of various side effects, which clarifies the need for more research on therapeutic modalities [58].

Music can help to reduce anxiety in animals [59] and humans [60]. Research has shown that physiologic markers of stress in humans were improved after a music therapy intervention [60]. Also, there have been putative effects of music on learning and memory. Evidence has increasingly proved that spatial learning and working memory acquisition and retention in mice, rats, and humans, are ameliorated by exposure to music[61]. Merely by listening to music, more regions of the brain are stimulated from the brainstem to the frontal cortex compared to any other activity[28]. Yao et al. found that Mozart's K.448 can improve the electrical activities of neurons of hippocampal CA1, which is an important part of emotional, behavioral, learning, memory, and other high-level neural activities[33]. Another report has indicated the brain development and neuroplasticity by mechanisms that involve facilitated hippocampal neurogenesis, neurotrophin synthesis, and glutamatergic signaling was modulated by exposure of music in rodents[62].

Previous studies reported that Music exposure results in increased rodents' spatial learning and memory [63]. One study examining retrograde versions of Mozart K.448 showed adverse effects that on spatial memory. This effect was also present when rodents heard music for the first time[32]. Our results indicated that music could not significantly improve spatial memory in PTSD rats. This discrepancy may have arisen from the difference in duration of music exposure.

4. Conclusions

In summary, our findings indicated that SPS, as a model of PTSD induction in rats, caused anxiolytic behaviors and learning and memory impairments in rats. Furthermore, exposure to music significantly improved and ameliorated these impairments. This is the first study indicating the efficacy of music in an animal model of PTSD. In our study, the mechanism by which music alleviated the impairments induced by SPS in rats is not studied. Further studies examining the neural mechanisms underlying the effect of music in the treatment of PTSD are needed for a better understanding of the pathophysiology of PTSD and the development of novel therapeutic strategies for PTSD.

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Conflicts of Interest

The authors declare no conflict of interest.

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