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Research Article

Classical Music and Environmental Enrichment Enhanced Spatial Memory and Learning and Increased Mouse Innate Tendency to Avoid Open Spaces

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Abstract

Little is known about combined effects of environmental enrichment and music stimulation on mice spatial learning and memory and on its innate repertoire to avoid open spaces. To investigate this question, 3 months aged BALB/c mice subjected to an environmental enriched (EE) or to an impoverished standard laboratory cage (IE) were exposed to random classical music (CM), three times a week, 12 h/day, three months, during the dark cycle, with an intensity of 65 dB. These groups were compared to control maintained in IE or EE but not exposed to music. All mice were then tested at the elevated plus maze (EPM), open field (OF) and Morris water maze (MWM). All tests were video recorded and analyzed using the Any-Maze®. A contrast index measured the relationship between the time spent in the periphery and the center of the open arena and between the closed and open arms of the EPM, and two-way ANOVA of these indices, showed significant influence of environment and music on the natural tendency to avoid open spaces. Of interest, was the significant increase in the time spent in the EPM closed arms of the EE/CM. All mice learned how to find and recall the hidden platform position before 7 days training. However, music stimulated EE mice, learned and recall the platform location faster than all other groups. In the open field test, it was found that the sound stimulus did not affect the locomotor behavior of these animals. Thus, the combination of an enriched environment and classical music stimulation seems to interact and enhance spatial learning and memory and increase the natural tendencies of BALB/c young mice to avoid open spaces.

Keywords: *Classical Music; Enriched Environment; Spatial Learning And Memory; Open Field; Elevated Plus Maze; Morris Water-Maze*

Introduction

It is already known that music intervention improve spatial memory and learning in experimental animals enhancing BDNF expression on dorsal hippocampus [1]. with long term effects on rescue of age-related deficits in spatial navigation tasks according to its duration [2]. Microarray analysis to compare the gene expression profiles of the hippocampus and cortex between the mice with music-exposure and the naïve ones showed differential gene expression in these areas, and these genes were mainly associated with ion channel activity and/or synaptic transmission, cytoskeleton, development, transcription and hormone activity 2009 [3]. Proteomic analysis of rat serum identified two associated serum peptide peaks with music intervention, which were further sequencing identifying differential expression of Desmin and Acsm1 proteins in male and [4].

In addition, structured, non-ethological sound stimuli have been used to study hippocampal plasticity in mouse e.g. [5]. These studies used a variety of sound stimuli including new-age-type music [6], Mozart KV 448 piano sonata, and compared these structured sound stimuli with noise or silence and tested as potential neurogenesis and neurotrophins release inductors on mice hippocampus. Kirste *et al.* [5] recorded pattern acoustic evoked potentials to the sonata to confirm audibility and found except by the noise, that sound stimuli and silence increased cell proliferation [5]. Further studies showed that in contrast to white noise, structured music sounds seems to up regulate BDNF levels in the pre-frontal, amygdala and hippocampus of humanized transgenic BDNF Met/Met knock in transgenic murine model of anxiety related behaviors unresponsive to serotonin reuptake inhibitors [7] Finally, exposure of mice to classical music for 1 month followed by behavioral assessment showed improvement of spatial learning and memory and elevation of fear-motivated memory in the mice with music-exposure as compared to the naïve mice and transcriptomic analysis of CNS areas of these mice, demonstrated 256 up and 181 down regulated genes in the hippocampus [3]. Similarly, proteomic study in correlation with rat's Morris water maze performances and music intervention demonstrated that music may plays a an important role in spatial learning and memory and this is associated with Desmin protein expression [4,8,9].

Other recent reviews were dedicated to discuss at different analytical levels (molecular, cellular and behavioral), the experience-dependent hippocampal plasticity [8-14] comparing contrasting environments, including wild and captive animals, or artificially impoverished and enriched cages. To our knowledge so far, none of these reviews or other original reports identified or described potential addictive interactions between music and environmental enichment.

Thus, we combined structured sound stimuli (music) and environmental enrichment and search for potential changes in the outcomes of BALB/c mice in hippocampal-dependent tasks.To that end, we selected hippocampal-dependent tasks that may involve both dorsal [15-17] and ventral hippocampal functions [18-21]. Open field and elevated plus maze mice outcomes leave apparent the avoidance drive individuals might show when exploring open spaces and they can be considered tests of natural preference for unlit and/or enclosed spaces [22], whereas water maze task outcomes may leave apparent spatial learning and memory [23]. In the present report the outcomes of BALB/c adult mice in these tasks were investigated to assess potential interactions of environmental enrichment and structured non-ethological sound stimuli (several pieces of classical music).

Methods

Animals

Thirty-two female BALB/c mice at 21st postnatal day were obtained from the animal house of the Evandro Chagas Institute. They were handled according to the "Principles of Laboratory Animal Care" (NIH) at the Laboratory of Investigations in Neurodegeneration and Infection at the University Hospital João de Barros Barreto, Federal University of Pará (LNI/HUJBB/ICB/UFPA). The project was approved by the Ethics Committee on the Use of Animals (CEUA/UFPA, nº 2472060218).

Accommodation

The animals were kept in a temperature-controlled room (23 ± 2°C) under a light dark cycle regime of 12 hours, with free access to water and food until 120 days of life. Standard animals (IE) were kept in standard laboratory cages (49 x 34 x 18cm), containing 8 animals per cage, limited to social interactions (without toys or running wheels). Enriched cages (EE), with two floors (100 x 50 x 100cm) built in iron and wire, containing wheels and movable bridges and toys of different shapes, sizes and colors, made of plastic, wood or metal. The toys were changed or relocated every 15 days. Food and water were offered on different floors, requiring systematic change to get them. Each enriched cage housed 8 individuals. Thus, the animals were divided in four groups: standard environment without music (IE-NM), standard environment with classical music (IE-CM), enriched environment without music (EE-NM) and environment enriched with music (EE-CM).

Sound stimuli

Diverse musical pieces of various classical music composers including Bach, Chopin, Dimitri Shostakovich, Edvard Grieg, Igor Stravinsky, Joseph Haydn, Ludwig van Beethoven, Mozart, Tchaikovsky and Vivaldi were reproduced around 65dB intensity levels. The classical songs remained for 12 hours, with a 10-minute of silent interval, every 30 minutes of music. Animals were exposed three times a week during the dark cycle, three months on alternated days.

Behavioral testing

At the 120^{th} postnatal day, all subjects were submitted to behavioral tests in the following order: Open Field, Elevated Plus Maze and Morris water maze.

Open field

The apparatus consists of a dark box (40 x 30 x 30 cm) with its floor virtually divided into nine quadrants. Animals were placed in the center of the arena and left in the open field for 5 minutes. Each animal had a single individual entry into the apparatus. The following parameters were analyzed: total traveled distance (m), immobility (s), number of crossed lines and time in the center x periphery [$C = (T_p - T_c) / (T_p + T_c)$], where C = contrast, T_p = time spent in the periphery, T_c = time spent in the center of the apparatus. Periphery and center of the open arena had equal areas. After each individual session the apparatus was cleaned with 70% alcohol to remove dirt and olfactory cues.

Elevated plus maze

Consists of two open arms and two closed arms (50 x 10cm) placed in opposite positions, and a central platform (10 x 10cm) (Lister, 1987). The closed arms have walls 40cm high, while open arms had no walls. The animal is placed on the central platform, loose with the face facing one of the open arms, allowing exploration of the environment for 5 minutes. The test in one day, with each animal performing one training session per day. At the end of the test the apparatus is cleaned with a 70% alcohol solution. The total distance traveled (m), still time (s), time in the open arm x closed (contrast) and time in the center of the apparatus were analyzed.

Morris water maze

The apparatus consisted of a dark blue pool filled with dark water dyed with edible powdered aniline to avoid viewing the platform that remained hidden 1cm below the surface of the water. The task followed previous protocol published elsewhere (Morris, 1984) adapted for mice. The water temperature is 23 ± 2°C. At each attempt, the animals will have time from 90s to find the hidden platform. Between each attempt there is an interval of 90s. A webcam located 2m above of the apparatus and connected to a computer system recorded all behavioral tests. Images were analyzed with ANY-maze software (Version 5.26, 2017 - Stoelting Co.).

The task was considered complete when the animal encounters the platform and remains there for five seconds. The first day will be devoted to the adaptation and training of the mouse to the aquatic labyrinth, where the animals that did not find the platform were led to her, and in the following days the escape latency (s) and the learning rate defined as contrast values as follows: $C = (LD_1 - LD_n) / (LD_1 + LD_n)$, where C is contrast and Ld_1 and Ld_n is average latency at the first day and LD_n are latency values on subsequent days.

Statistical analysis

Experimental groups were compared using two-way ANOVA, Bonferroni a priori tests, with confidence levels at 95 or 99% of confidence ($p < 0.05$ or $p < 0.01$).

A contrast index was used to compare measurements of time spent in the open and closed arms of EPM and periphery and center of the open arena in the open field task.

$$C = (C1 - C2) / (C1 + C2)$$

Where:

C = Contrast Index

C1 = time spent in OF periphery or time spent in the closed arm of EPM

C2 = time spent in OF center or time spent in the open arm of EPM

Results

Open field

Significant influence of the environment was found in travelled distance ($F_{1,59}$ = 8.259, p < 0.0056), where EE-NM *vs* IE-NM, where EE-NM showed on average, higher values of travelled distance than IE-NM, *p < 0.0003. Figure 1A (mean and standard error values) and Figure 1E (occupancy plot) illustrate these results, however, the interaction between environmental and sound stimuli ($F_{1,59}$ = 4.905, p < 0.03) changed this result in the music groups where no differences were found anymore. Important to highlight however that simultaneous comparisons between the time spent in the peripheral and center zones of the open arena showed significant influences of environment ($F_{1,59}$ = 14.42; p < 0.0003) and music ($F_{1,59}$ = 4.01, p < 0.0498), experimental variables, but no interactions between them (Figure 1D). These findings suggest these variables, act differentially in the animal groups, where the EE-CM animals occupied the center of the apparatus longer than IE-CM animals (AP-CM *vs* AE-CM, **p < 0.0021). Immobility (Figure 1C), was influenced by sound stimuli, ($F_{1,59}$ = 2.118, p < 0.0133), but no significant differences were found in the post-test analysis.

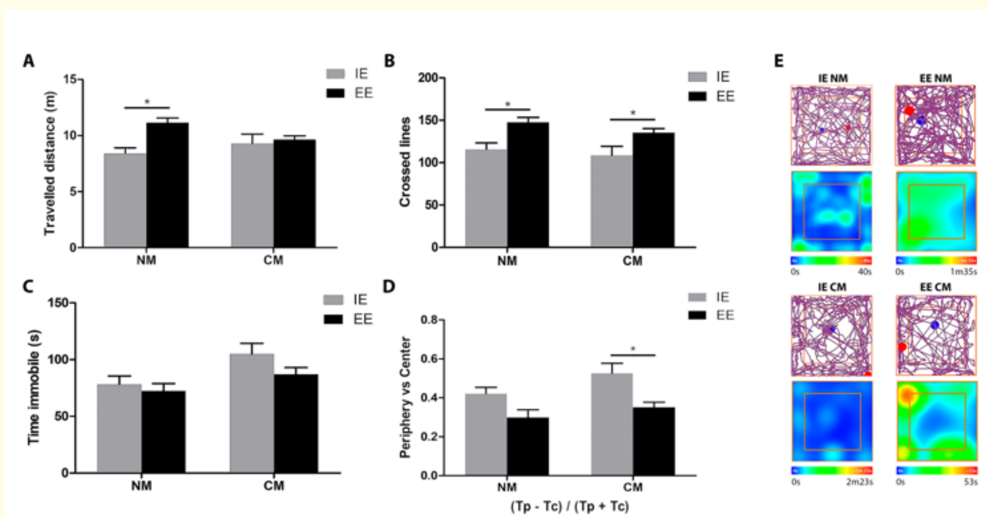

Figure 1: *BALB/C Mice Outcomes In The Open Field Task Under Influence Of Environmental Enrichment And Music Stimuli. A) Travelled Distance. B) Crossed Lines. C) Immobility And D) Contrast Index Between Time Spent In The Periphery And Center, C = (Tp - Tc)/(Tp + Tc), Where C Corresponds To Contrast And Tp And Tc Correspond To Time Spent In The Periphery And In The Center Regions. Periphery And Center Regions Of The Open Arena Had Equal Areas. E) Trajectories And Heat Plots Exhibit The Occupied Areas. NM = No Music, CM = Classic Music, IE = Impoverished Environment, EE = Enriched Environment. Color And Time Scales Are Indicated Below Heat Plots.*

Elevated plus maze test

The EPM test (Figure 2) was applied to investigate potential influences of environment and sound stimuli of classical music pieces on natural preferences of open and closed spaces and in the way, mice assess risk. Music and environment interact and changed the results of contrast index ($F_{1,58} = 33.55$, $p < 0.0001$), with significant influence of environment and sound stimuli The analysis of the time in the open arm x closed arm (Figure 2A), obtained by the equation [(IC = (C1 - C2) / (C1 + C2)], where C1 is the time in the closed arm and C2 is the time in the open arm, revealed that the music and environment stimulus had interaction ($F_{1,58} = 33.55$, $p < 0.0001$). Indeed, as compared with IE-SM group, EE-NM group spent longer time in the open arm (IE-SM vs. AE-NM, **p < 0.0005). Importantly, sound stimuli and enriched environment in combination (EE-CM) reverted this tendency, showing significant increase in the time spent in the closed arm (EE-NM *vs* EE-CM, $^{\#}p < 0.0001$ and IE-CM *vs* EE-CM, *p < 0.0011). Figure 2B shows trajectories and occupancy plots. Notice that the EE-NM occupied all regions of the EPM arms, while EE-CM mostly avoided open arms, spending larger amount of time inside closed arms.

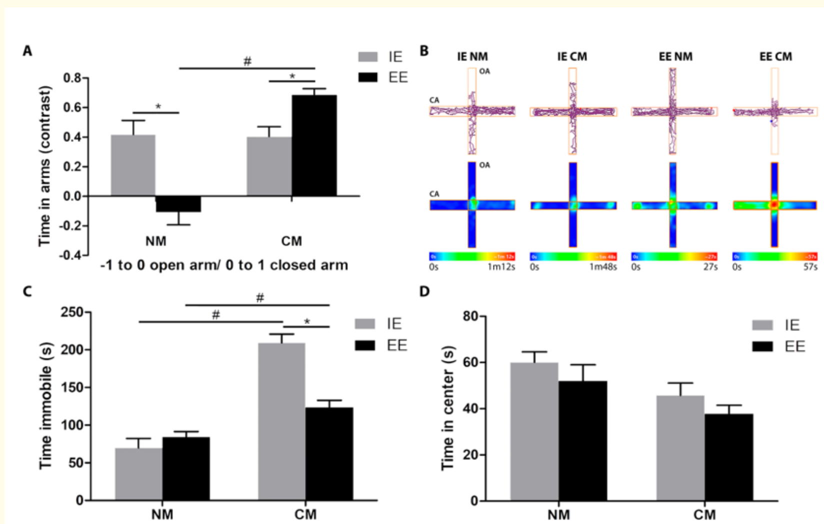

Figure 2: *BALB/C Mice Outcomes In The Elevated Plus Maze Task Under Influence Of Environmental Enrichment And Music Stimuli. A) Contrast Index Between Time Spent In Closed And Open Arms. C = (Tca - Toa)/(Tpca + Toa), Where C Corresponds To Contrast And Tca And Toa Correspond To Time Spent In The Closed And In The Center. Note That Environmental Enrichment In Isolation Reverse The Natural Tendency To Avoid Open Spaces And That Combined Classic Music And Environmental Enrichment Enhanced Natural Tendency To Avoid Open Spaces. B) Color And Time Scales Are Indicated Below Heat Plots. C) Immobility Is Strongly Affected By Music Independent Of The Environmental Changes But No Significant Changes Were Observed In The Time Spent In The Central Platform (D). NM = No Music, CM = Classic Music, IE = Impoverished Environment, EE = Enriched Environment.*

Figure 2C shows for how long mice became immobile in the EPM compartments. Environment and sound stimuli of classical music pieces interact and changed the amount of time mice became immobile ($F_{1,58} = 17.62$; $p < 0.0001$), increasing immobility of sound stimuli group (IE-NM *vs* IE-CM, $^{\#}p < 0.0001$ and EE-NM *vs* EE/CM, $^{\#}p < 0.01$). Yet, IE and EE groups were differentially affected by sound stimuli (IE - CM *vs* EE - CM, $^{**}p < 0.0001$). Although no differences were detected in the post-tests, the time spent in the central platform was affected by sound stimuli ($F_{1,58} = 6.83$; $p < 0.01$).

Water maze task

One-way ANOVA compared escape latencies of the first day test with all other day tests to find in what test day differences became significant taking the first day as the reference point. We found that the best learning rate was obtained by the group maintained in enriched environment submitted to sound stimuli. Indeed, on average, EE-CM individuals had the highest learning rate. They learned and recalled the position of the hidden platform on the 2nd day training (1st *vs* 2nd training day, $p < 0.006$). This group was followed by EE-NM (1st *vs* 3rd, $p < 0.01$), IE-CM (1st *vs* 4th, $p < 0.005$) and IE-NM (1st *vs* 5th, $p < 0.028$); figure 3.

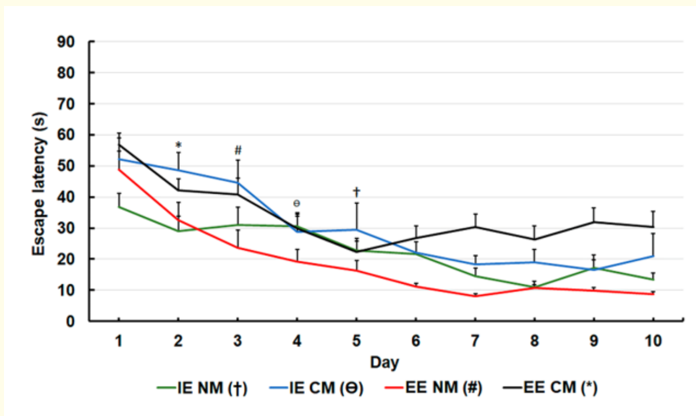

Figure 3: *BALB/c Mice Outcomes In The Water Maze Task Under Influence Of Environmental Enrichment And Classical Music Stimuli. Learning Rates Progression Are Depicted By Color Lines. Note That EE CM (Black Line) Showed Significant Difference In The 2nd Training Session, While All Other Experimental Conditions Took Longer Time To Learn And Remember The Hidden Platform Position. Indeed, As Compared To The 1st Training Day, IE CM (Blue Line), EE NM (Red Line) And IE NM (Green Line) Reached Significance At The 3rd, 4th And 5th Day Respectively. NM = No Music, CM = Classic Music, IE = Impoverished Environment, EE = Enriched Environment.*

We also assessed the learning rate using a contrast index between the escape latency of the 1st day and the escape latency of all subsequent training days as follows: $C = (L_{1st} - L_n)/ (L_{1st} + L_n)$, where C = contrast, $L1_{st}$ = escape latency of the first day and L_n = escape latency of the subsequent days. Two-way ANOVA of these indices demonstrated significant influence of environment ($F_{1,354} = 19.1$, $p < 0.0001$) and of the sound stimuli ($F_{1,354} = 6.06$, $p < 0,001$) and these two variables interacted addictively and change the result ($F_{1,354} = 2.05$, $p < 0.02$).

Discussion

It is well known that environmental conditions can exert a significant influence on brain development, behavior and neuroplasticity. It is also known that music also induces hippocampal neuroplasticity. Here we tested the hypothesis that environmental enrichment and classical music would interact and affect behavioral outcomes of classical hippocampal-dependent tasks using an adult BALB/c murine model. We found addictive influences of music and environment on spatial learning and memory outcomes, and subtractive, addictive or no interactions between these variables on the natural preference by closed/unlit spaces.

Dorsal and ventral hippocampus, spatial learning and memory and natural preferences for closed/unlit spaces.

Various studies have shown anatomical and functional differences between the dorsal (DHC) and ventral (VHC) portions of this structure: DHC lesions impair spatial learning [24], whereas VHC lesions, reduce anxiety and fear expression [25-27]. The DHC is primarily involved in spatial navigation and contains cells with small place fields. The VHC is primarily involved in context and emotional encoding, contains cells with large place fields, and receives major projections from the medial prefrontal cortex [28]. A dorsal-ventral asymmetry in transcription and methylation that parallels functional and anatomical differences is enhanced by environmental enrichment [17].

Here we demonstrated that spatial memory which seems to be part of the dorsal hippocampus repertoire has been influenced with an addictive interaction where combined music stimuli and environmental enrichment were associated with the best learning rate, while impoverished environment and no music showed the worse learning rate. Because no previous data combining enriched environment and music intervention are available we cannot compare our findings with other reports. However, it is reasonable to raise the hypothesis that the observed addictive effect on spatial memory and learning can be a consequence of dorsal hippocampus associated changes as separately demonstrated for enriched environment [17] and music intervention [1]. On the other hand, open field and elevated plus maze outcomes were either subtractive or addictively affected by the same combined stimulation. Indeed, environmental enrichment alone reversed, the mouse natural tendency of avoiding open arms in the EPM tasks, whereas the combination between environmental enrichment and music, increased the natural tendency to avoid open arms. In the open field however, sound stimuli on mice from impoverished environment of standard laboratory cage, increased the natural tendency to avoid open spaces while environmental enrichment in combination with classical music pieces reverse this tendency up to normal levels.

Because elevated plus maze is mainly related to ventral hippocampus activity through CRF1 receptor and PKA pathway [29] and open field task seems to involve both dorsal and ventral hippocampus activities [19,30] we suggest that the differential effects of music intervention and enriched environment on the outcomes may be consequence of distinct hippocampal regional stimulation [31,32]. Thus, we suggest that ventral and dorsal hippocampus may be affected by structured non-ethological musical stimuli and environmental enrichment and these influences may interact subtractive or addictively depending on the hippocampal function requested to accomplish the task.

Conclusion

We demonstrated that combining music stimuli and environmental enrichment was associated with better learning and spatial memory, indicating an addictive effect of enriched environment and classical music stimuli. In addition, an increase in the natural tendencies of BALB/c mice to avoid open spaces were observed suggesting that both the dorsal and ventral hippocampus are involved in the associated behavioral changes.

Compliance With Ethical Standards

All animals were handled according to the "Principles of Laboratory Animal Care" (NIH) at the Laboratory of Investigations in Neurodegeneration and Infection at the University Hospital João de Barros Barreto, Federal University of Pará (LNI/HUJBB/ICB/UFPA). The project was approved by the local Ethics Committee on the Use of Animals (CEUA/UFPA, nº 2472060218).

Conflict of Interest

All authors have no conflict of interest.

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