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Research report

Music exposure improves spatial cognition by enhancing the BDNF level of dorsal hippocampal subregions in the developing rats

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ABSTRACT

Previous research has shown that dorsal hippocampus plays an important role in spatial memory process. Music exposure can enhance brain-derived neurotrophic factor (BDNF) expression level in dorsal hippocampus (DH) and thus enhance spatial cognition ability. But whether music experience may affect different subregions of DH in the same degree remains unclear. Here, we studied the effects of exposure to Mozart K.448 on learning behavior in developing rats using the classical Morris water maze task. The results showed that early music exposure could enhance significantly learning performance of the rats in the water maze test. Meanwhile, the BDNF/TrkB level of dorsal hippocampus CA3 (dCA3) and dentate gyrus (dDG) was significantly enhanced in rats exposed to Mozart music as compared to those without music exposure. In contrast, the BDNF/TrkB level of dorsal hippocampus CA1 (dCA1) was not affected. The results suggest that the spatial memory improvement by music exposure in rats may be associated with the enhanced BDNF/TrkB level of dCA3 and dDG.

1. Introduction

The brain has the remarkable capacity to alter in response to environmental demands. Training-induced structural brain changes have been demonstrated in the healthy and pathological brain (Hyde et al., 2009). Music is well known to affect biological systems and is used to regulate mood and arousal in everyday life, and then to promote physical and psychological health in clinical settings. The neuroplasticity changes induced by specific musical training have been studied in childhood or neurological population (Clément et al., 2015). Studies have suggested that listening music can enhance ability in related areas, particularly spatial cognition. Rauscher (1993) reported that undergraduates who listened to Mozart Sonata K.448 showed significant improvement in a spatial-temporal task when compared to control subjects who listened to something else or silence. The auditory stimulation (including music) received early in life enhances both sub-cortical and cortical electrophysiological responses to sounds (Kraus and Chandrasekaran, 2010) and persists in adult development (White-Schwoch et al., 2013). Early musical training is linked to gray matter structure in the ventral premotor cortex and auditory-motor rhythm synchronization performance (Bailey et al., 2014). Children with music training demonstrated better verbal memory than their counterparts without such training (Ho et al., 2003). Similarly, animal experiments also found that music improves spatial performance in the rats (Rauscher et al., 1998). These findings indicate the possibility that music has some effects on neuronal plasticity that is more efficient at early developmental stages.

Brain-derived neurotrophic factor (BDNF) and its receptor TrkB are known to play a critical role in the synaptic plasticity underlying the acquisition and/or consolidation of certain forms of memory in both the developing and adult mammalian central nervous system (Tyler et al., 2002; Heldt et al., 2007). Correlational studies show that BDNF expression is increased in hippocampal-dependent tasks (Hall et al., 2000). Spatial learning induces BDNF and TrkB expression in activated brain areas (Mizuno et al., 2000; Gomez-Pinilla et al., 2001). Exposure to Mozart music in the perinatal period alters BDNF/TrkB signaling in adult mice hippocampus (Chikahisa et al., 2006).

Despite a very long history of research, there is still controversy over the basic general function of the hippocampus (Fanselow

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and Dong, 2010). Anatomical studies indicated that the input and output connections of the dorsal hippocampus (DH) and ventral hippocampus (VH) are distinct (Swanson and Cowan, 1977). A popular concept is that the DH preferentially contributes to spatial domains, while the VH plays a preponderant role in emotional processes (Moser et al., 1995). In addition, it has been found that DH lesions caused a deficit in spatial memory, VH lesions did not (Pothuizen et al., 2004). Anatomically, the hippocampus is composed of three main subregions: CA1, CA3 and dentate gyrus (DG) and there exists specificity of function for different hippocampus subregions. For example, DG subregion, in conjunction with CA3, supports spatial pattern separation; yet CA1 subregion supports temporal pattern processes (Kesner et al., 2004). But whether music exposure influences the expression level of BDNF/TrkB in different hippocampal subregions in the same degree remains unclear.

The Morris water maze (MWM) task is one of the most robust measures of hippocampal functioning (D'Hooge and Deyn, 2001). To better characterize the diversity of functions associated with dCA1, dCA3 and dDG, here we investigated the expression level of BDNF/TrkB of DH subregions in learning and memory of developing rats using the MWM test. We also examined whether enhanced spatial memory is associated with music exposure. Furthermore, we discussed the relationship between the BDNF/TrkB protein expression level of hippocampal subregions and spatial memory.

2. Materials and methods

2.1. Animals preparation

Male Sprague Dawley adult rats (250 ± 10 g) and female Sprague Dawley adult rats (180 ±10 g) were purchased from Animal Research Institute (Sichuan, China) and self-reproduction. 30 newborn rats were randomly divided into two groups: Mozart group (MG, exposure to Mozart K.448, $n = 15$) and control group (CG, without music exposure, $n = 15$). The rats were housed in five per cage under standard conditions of humidity and room temperature, and a 12-h light/dark cycle (lights on at 08:00 h). The rats had free access to water and food.

All experiments were performed according to the experimental guidelines of the University of Electronic Science and Technology of China, and the experimental protocol was approved by the ethics committee of the University of Electronic Science and Technology of China.

2.2. Music exposure

Music group rats were exposed to Mozart's piano sonata K.448, which is usually used in studies on the "Mozart effect", from the postnatal day (PND) 1 and to PND 98. Music was repeated daily continuously for 12 h starting from 8.00 p.m. to 8.00 a.m so that the rats would not be disturbed in their sleep. The sound level of Mozart's music was 65 ~ 75 dB and ambient noise was 65 dB.

2.3. Hidden-platform Morris water maze

In the MWM task, a convenient and popular test of cognitive function in rodents, the rat uses spatial clues while swimming to locate a submerged platform. The MWM consisted of a circular pool made of white PVC plastic with 50 cm high walls and a diameter of 130 cm. The maze was filled to a depth of 25 cm with 26 °C water which was made opaque by the addition of white, thick, nontoxic milk. The pool was virtually divided into four equivalent quadrants: target quadrant, left quadrant, right quadrant and opposite quadrant. A small clear Plexiglas escape platform (10 cm diameter) was placed at a fixed position in the center of target quadrant and was hidden 2 cm beneath the water surface. The MWM was placed in a sound-isolated testing room, illuminated by normal housing lights and surrounded by a number of fixed extra maze cues.

All rats were tested three times on P28, P56, and P98. The acquisition phase consisted of four consecutive training days (sessions) with four trials per day, starting at four different positions in a random order. One day before each testing period, all rats received a pretraining session in order to habituate the training environment. In the pretraining session, each rat was placed in the pool for 120 s, and then allowed to climb onto the platform where it could rest for 20 s. On each trial, rats were placed in a starting location facing the pool wall and allowed to swim until finding a submerged platform or until a maximum of 60 s. On finding the platform, rats remained on the platform for 20 s. If they failed to escape within 60 s rats were guided to the platform and allowed to stay on the platform for 20 s. Rats remained in retaining cage for 60 s before the start of the next trial or the return to home cage at end of training session. One day after the acquisition phase, each rat was given a probe session. During this session, the platform was removed from the maze and the rats were allowed to swim freely for 60 s.

The performance of the rats in the MWM task (including latency time to escape, time spent in each quadrant) were recorded by a video camera and quantified using WMT-200 software. The latency time from immersion into the pool to escape onto the platform was recorded to provide a measure of spatial reference memory for each trail (four trails a day, total 16 trials for each rat). Time spent in each quadrant was measured (% total time, chance level = 25%).

2.4. Immunohistochemical analysis of BDNF and TrkB

Rats were anesthetized and transcardially perfused with 4% paraformaldehyde fixative at the end of each behavior test (PND 28, PND 56 and PND 98, $n = 5$ per group at each time point). Then they were rapidly decapitated and their hippocampi were removed and placed in the same fixative for 24 h before being transferred into a 30% sucrose solution for cryoprotection. Samples were serially sectioned in the coronal plane at 30 μm using a freezing microtome (Leica, Nussloch, Germany).

The free floating sections were processed for immunohistochemistry (IHC) as previously described (Lemaire et al., 2000). Briefly, for antigen retrieval, sections were incubated with 0.25% trypsin in phosphate-buffered saline (PBS) for 5 min. Following extensive washes in PBS, the sections were blocked with 10% goat serum solution for 1 h. Primary antibodies were applied overnight at 4 °C. The sections were then washed three times with PBS and incubated for 1 h with a species-specific secondary antibody. Subsequently, the sections were extensively washed again and placed on superfrost Plus slides. After mounting, the sections were observed and photographed using a Leica microscope equipped with a Spot® digital camera.

The following antibodies and final dilutions were used. The primary antibodies included: rabbit anti-BDNF (1:200, Santa); rabbit anti-TrkB (1:200, Abcam). For corresponding secondary antibodies, goat anti-rabbit (1:200, Southern Biotech) were used.

2.5. Statistical analysis

Statistical analyses were performed using statistical software SPSS (version 16.0). For behavioral tests, the escape latency of hidden-platform acquisition training was analyzed with a repeated measures analysis of variance (ANOVA) with a general linear model. Group differences in the duration of time spent in quadrants were analyzed with one-way ANOVA.

For the IHC, the area in the selected region was measured using Image-Pro Plus software (Media Cybernetics, Silver Spring, MD). A one-way ANOVA was used to evaluate relative levels of BDNF/TrkB