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Parasympathetic activation is involved in reducing epileptiform discharges when listening to Mozart music

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H I G H L I G H T S

- Listening to Mozart's K.448 and K.545 reduced epileptiform discharges in epileptic children.
- Heart rate variability analysis showed parasympathetic activation, significant increases in parasympathetic parameters, and a decrease in mean heart rate during listening to Mozart music.
- The results suggested that Mozart music stimuli induced parasympathetic activation which may be involved in the effect of music on epilepsy.

A B S T R A C T

Objective: Listening to Mozart K.448 has been demonstrated to improve spatial task scores, leading to what is known as the Mozart effect. Our previous work revealed the positive effects of Mozart K.448 in reducing epileptiform discharges in children with epilepsy. However, the mechanism remains unclear. parasympathetic activation has been shown to help seizure control in many studies. In this study, we investigated the effect of Mozart music on epileptiform discharges and autonomic activity.
Methods: Sixty-four epileptic children with epileptiform discharges were included. They all received electroencephalogram and electrocardiogram examinations simultaneously before, during, and after listening to Mozart K.448 or K.545. The total number of epileptiform discharges during each session (before, during, and after music) were divided by the duration (in minutes) of the session and then compared. Heart rate variability including time and frequency domain analysis was used to represent the autonomic function.
Results: The results showed that epileptiform discharges were significantly reduced during and right after listening to Mozart music (33.3 ± 31.1% reduction, $p < 0.001$, during Mozart K.448 and 38.6 ± 43.3% reduction, $p < 0.001$, during Mozart K.545) (28.1 ± 43.2% reduction, $p < 0.001$, after Mozart K.448 and 46.0 ± 40.5% reduction, $p < 0.001$, after Mozart K.545). No significant difference was noticed between the two pieces of music. The reduction was greatest in patients with generalized seizures and discharges. Significant increases in high-frequency (HF), the square root of the mean squared differences of successive RR intervals (RMSSD), the standard deviation of differences between adjacent RR intervals (SDSD), and a decrease in mean beats per minute (bpm) were found during listening to Mozart music. Most of the patients with reduced epileptiform discharges also showed a decreased LF/HF ratio, low-frequency normalized units (LF nu), mean bpm, and an increased high-frequency normalized units (HF nu).
Conclusions: Listening to Mozart music decreased epileptiform discharges in children with epilepsy. The majority of these patients showed an increase in parasympathetic tone during music exposure.

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Significance: Our results suggested that Mozart music stimuli induced parasympathetic activation which may be involved in the effect of music in reducing epileptiform discharges and the recurrence rate of seizures.

1. Introduction

Music has been used to improve physical and mental illnesses. Rauscher et al. first reported the "Mozart Effect" in 1993. They noted that Stanford-Binet spatial task scores improved immediately after listening to Mozart's Sonata for Two Pianos in D major, K.448 (Mozart K.448) for 10 min, when compared to the same time of silence or relaxation instruction (Rauscher et al., 1993). Regarding epilepsy, Hughes et al. and our previous study showed that epileptiform discharges decreased when patients with epilepsy listened to Mozart K.448 (Hughes et al., 1998; Lin et al., 2010). However, the mechanism of this music effect on epilepsy remains unclear. Music has been reported to significantly increase relaxation sensations and decrease fatigue sensations in treated cancer survivors (Chuang et al., 2010). An increase in parasympathetic nervous system activity and a decrease in sympathetic nervous system activity were found in these patients by heart rate variability (HRV) analysis (Chuang et al., 2010). Therefore, HRV can be considered as a marker of autonomic activation. HRV analysis is performed by detecting consecutive R wave to R wave intervals (RR intervals) between successive pairs of QRS complexes (a combination of three of the graphical deflections) during electrocardiography (EKG). The variations can be evaluated by time domain analysis or frequency domain analysis. In time domain analysis, either the heart rate at any point in time or the intervals between successive normal complexes are determined (Task force, 1996). In frequency domain analysis, variance distribution, as a function of frequency, is determined by power spectral density analysis (Task force, 1996).

A relationship between autonomic activity and regional brain activity has been found in recent neuroimaging studies. Parasympathetic activity, as measured by the high frequency component of HRV, is associated with the anterior cingulate cortex, bilateral cuneus, and parahippocampus during functional MRI (fMRI) tasks involving working memory and emotion (O'Connor et al., 2007). It is reported that various medical conditions are associated with lower parasympathetic tone, including diabetes, coronary heart disease, and epilepsy (Yuen and Sander, 2010). Mukherjee et al. reported that lower parasympathetic tone, lower parasympathetic reactivity, and more severe dysautonomia are found in patients with intractable epilepsy than in those with well-controlled epilepsy (Mukherjee et al., 2009). Our previous studies showed that listening to Mozart music reduced epileptiform discharges and seizure frequencies (Lin et al., 2010, 2011). However, the music effect mechanism in reducing epileptiform discharges is still unknown. In this study, we tested the hypothesis that increased parasympathetic activity participates in the reduction of epileptiform discharges when listening to Mozart music. The influences of loci of epileptiform discharges, mentality of the patients, state of wakefulness, etiology of epilepsy, seizure type, and gender were analyzed and discussed.

2. Patients and methods

2.1. Subjects

Sixty-four Taiwanese children (31 boys and 33 girls) diagnosed with epilepsy were enrolled. The mean age of these children was 7 years 10 months ± 3 years 1 month (ranging from 2 years 11 months to 15 years 4 month). The diagnosis of epilepsy was made according to the criteria established by the International League Against Epilepsy (ILAE). Informed consent was given by a family member or legal guardian in each case. This study was approved by the Institutional Review Board of Kaohsiung Medical University Hospital.

2.2. Electroencephalogram examinations

The patients in this study received electroencephalogram (EEG) examinations in three parallel periods; before, during, and after listening to Mozart K.448 (8 min 22 s) or K.545 (9 min 7 s) according to the patient's preference (as our unpublished data showed that both Mozart K.448 and K.545 reduce epileptiform discharges similarly). They received 60–70 dB of musical stimuli via loudspeakers (Arnon et al., 2006) that was measured with a decibel meter (DSL332, Taipei, Taiwan). Each EEG was recorded digitally using 21 electrodes (Harmonie DVN V5.1, Montreal, Canada). Electrodes were placed according to the International 10–20 System. The epileptiform discharges were defined as distinct waves or complexes, distinguished from background activity. Two neurologists counted the number of discharges in each of the three sections of the experiment. An example of epileptiform discharges calculation by visual inspection was demonstrated by Fig. 1.The total number of epileptiform discharges during each section (before, during, and after music) were divided by the duration (in minutes) of the section and compared. Changes in epileptiform discharge were expressed as ([baseline discharge − discharge during/after music]/baseline discharge) $\times$ 100. All recordings were performed during the daytime. To decrease the factors influencing epileptiform discharges, each patient maintained the same state of wakefulness throughout the recording period. The EEGs during the three section of the experiment were continuously monitored to ensure that a change of wakefulness did not occur. For an unbiased comparison of EEG, patients who had seizure attack during the recording period were excluded (Cabrerizo et al., 2011, 2012). In this article, the term "effective" was defined as patient exposure to music resulting in any reduction in epileptiform discharges.

2.3. Heart rate variability analysis

EEG and electrocardiogram (EKG) signals were collected simultaneously. The method used for data acquisition of EKG signals and signal analysis followed the standards of HRV (Task force, 1996). Consecutive RR intervals were measured by detecting R waves between successive pairs of QRS complexes. All artifacts or ectopic beats were removed through visual inspection. Similar to EEG analysis, the stationary RR intervals were divided into three stages for HRV analysis. In the time domain, the square root of the mean squared differences of successive RR intervals (RMSSD), the standard deviation of the RR interval (SDNN), the standard deviation of differences between adjacent RR intervals (SDSD), and the mean beats per minute (bpm) were used as the HRV measures for evaluating the effects of music listening.

In the frequency domain, a frequency band ranging from 0.04 to 0.15 Hz was defined as the low-frequency (LF) component, which was related to the regulation of blood pressure and reflected the