ORIGINAL ARTICLE:

Increased Brain Derived Neurothropic Factor in the cerebrum and cerebellum of *Rattus norvegicus* newborn with exposure to Mozart's music in default sequence compared with the reversed sequence and without exposure during gestation

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ABSTRACT

Objectives: To analyze the differences in the expression of Brain Derived Neurothropic Factor (BDNF) in *Rattus norvegicus* cerebrum and cerebellum of newborn between those exposed to Mozart's music composition in default sequence, reverse sequence, and without exposure in the womb.
Materials and Methods: Analytical laboratory experimental study with randomized post test only control group design using animal models *Rattus norvegicus*. The animal models were divided into three groups: control group without any exposure, the treatment groups with exposure to Mozart's music in default sequence and another group in reverse sequence since day 10 of gestation. We used a comparison test in the analysis of BDNF expression.
Results: We found significant difference in BDNF expression with p value 0.004 (mean 8.98±1.31 default sequence group, 5.58±3.08 reverse sequence group, 6.80±1.95 control) in the cerebrum. We found significant difference of BDNF expression with p value 0.003 (mean 9.48±1.41 default sequence group, 6.02±3.25 reverse sequence group, 7.14±2.54 control) in the cerebellum. In cerebrum dan cerebellum we found significant difference between standard Mozart's music and control (cerebrum p=0.018, cerebellum p=0.001), and we found significant difference between standard Mozart's music and reverse Mozart's music (cerebrum p=0.001, cerebellum p=0.008) and no significant difference in reverse Mozart and control (cerebrum p=0.264, cerebellum p=0.490)
Conclusion: Sequence in Mozart's music is very important in increase expression of BDNF.

Keywords: IUCD postplacental, caesarean delivery, puerperial period, postpartum bleeding, infection

ABSTRAK

Tujuan: Untuk menganalisis perbedaan pada ekspresi Brain Derived Neurothropic Factor (BDNF) pada cerebrum dan cerebellum neonatus *Rattus norvegicus* antara yang terpapar komposisi musik Mozart dalam urutan standar, urutan terbalik, dan tanpa paparan di dalam uterus.
Bahan dan Metode: Penelitian eksperimental laboratorium analitik dengan desain post-test only control group menggunakan model hewan *Rattus norvegicus*. Model hewan dibagi menjadi tiga kelompok: kelompok kontrol tanpa paparan, kelompok perlakuan dengan paparan musik Mozart dalam urutan standar dan kelompok lain dalam urutan terbalik sejak hari ke 10 kebuntingan. Kami menggunakan uji perbandingan pada analisis ekspresi BDNF.
Hasil: Terdapat perbedaan signifikan pada ekspresi BDNF dengan nilai p 0,004 (rerata 8,98±1,31 pada kelompok urutan standar, 5,58±3,08 kelompok urutan terbalik, 6.80±1.95 kontrol) pada cerebrum. Terdapat perbedaan signifikan pada ekspresi BDNF dengan nilai p 0.003 (rerata 9.48±1.41 kelompok urutan standar, 6.02±3.25 kelompok urutan terbalik, 7.14±2.54 kontrol) pada cerebellum. Pada cerebrum dan cerebellum terdapat perbedaan signifikan antara musik Mozart kontrol dan standar (cerebrum p=0.018, cerebellum p=0.001), dan terdapat perbedaan signifikan antara musik Mozart urutan standar dan terbalik (cerebrum p=0.001, cerebellum p=0.008) dan tidak ada perbedaan signifikan pada musik Mozart urutan terbalik dan kontrol (cerebrum p=0.264, cerebellum p=0.490).
Simpulan: Urutan dalam musik Mozart sangat penting dalam meningkatkan ekspresi BDNF.

Kata kunci: IUCD post-plasenta, kelahiran caesar, masa puerperial, perdarahan postpartum, infeksi

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INTRODUCTION

During development in the womb is the most amazing time in a phase of human development. The development of knowledge and the number of studies show that this phase depends not only genetic factors, but the fetal environment also influenced the development of the functional capacity of organs, especially the brain. It can be concluded that when the pregnancy is the right time to set up the potential of intelligence from an early age. Among the efforts to promote growth and brain development early on is to provide adequate nutrition and stimulation during pregnancy. Stimulation of the most easily accepted fetus is sound and music is a combination of the most harmonious sound.[1]

In the womb, the brain cell proliferation, migration, and apoptosis synaptogenesis. Gilbert et al found that the number of cells has not increased since about 32 weeks gestation. Volpe et al stated that the ability neurobehaviour baby at 32 weeks did not differ with the term infant. Bures et al and many other scholars have found that brain structure is formed by external stimuli, known as the premise: Stimulation induced morphological changes.[2]

Brent Logan argues that the noise is one of the factors on the basis that the growth of the fetus in the womb is always there sounds including heart rate, intestinal peristalsis and mother's voice. While fetal ears can already be hear perfectly since the age of 18 weeks, so it has been established lines of communication between the fetus, the mother and the outside world through sound, even music.[3]

Neurothrophic theory explains that the survival of neurons depends on factors neurothrophic, said also that neuronal cell death triggered by a limited number of these neurothrophic factor with consequent loss of cell survival signals.[4,5] Neurothropin, including that NGF, BDNF, NT-3 and NT-4, a protein that plays an important role in the growth of neuronal cells, especially in controlling the loss of neuronal cell development.[4] Brain-Derived Neurothropic Factor (BDNF), is one member of the family of Nerve Growth Factor (NGF). In addition to NGF and neurothropin (NT), BDNF has an important role in regulating apoptosis, proliferation. 37 BDNF is a holder of a role in the development of brain cells due to its ability to protect brain cells from a variety of pathological conditions).[6] BDNF affect the number of cells glia and neurons.[7]

Aryananda study (2016) found an increase in BDNF and obtained an increase in the number of neurons and oligodendrocyte in the cerebrum *Rattus norvegicus* receiving exposure to Mozart's music raw sequence. Other studies put forward by Marcianora (2016) that increased BDNF affects the density of the dendrite in the cerebrum and cerebellum.[8,9] Stimulation of music is a tool that is cheap, effective and rational. On the basis of previous studies developed further research is finding the right formula to provide stimulus to the music on the fetus. By providing a stimulus early on pregnant or after pregnancy 20 weeks after the hearing organ formed.

Ismudi (2007) have compared the three compositions Mozart (I, II, III) and is associated with brain cell apoptosis index. The composition obtained Mozart I, which has the lowest value index of apoptosis. However, further research by Habibie (2017) is not found significant differences of the apoptotic index *Rattus norvegicus* newborn between who gets exposure to Mozart order raw and upside down, but the average value of apoptotic index in Mozart group in default sequence had lower scores than the Mozart group with reverse sequence and both at the cerebrum controls and cerebellum.[10,11,12]

This study is a continuation of a series of studies to educate the baby in the womb aims to determine how the influence of Mozart's music if it was exposed in reverse order on the expression of BDNF in *Rattus norvegicus*.

MATERIALS AND METHODS

This study was a randomized design laboratory experimental with post test only control group design using animal *Rattus norvegicus*. The subjects were divided into three groups randomly, group I was *Rattus norvegicus* getting exposure to Mozart's music default sequence for 1 hour in the evening, group II is *Rattus norvegicus* getting exposure to Mozart's music in reverse sequence for 1 hour in the evenings and group III (control) *Rattus norvegicus* are not getting exposure to Mozart's music. The study was conducted in the Cage Animal Try and Pathology Laboratory of the Faculty of Veterinary Medicine, Airlangga University Surabaya, during the months of October to December, 2016.

The inclusion criteria are holding pregnant *Rattus norvegicus*, 2 months old, 120-150 grams body weight, and the newborn *Rattus norvegicus*, while the study exclusion criteria are *Rattus norvegicus* mothers with anatomical abnormalities and pain before treatment. Drop-out criteria *Rattus norvegicus* test that is the mothers of pain during treatment, *Rattus norvegicus* offspring dies in the womb or were born before the 19th day of gestation.

The sample size was calculated using the formula Federer, and found the number of samples per group obtained by 9. Each pregnant *Rattus norvegicus*, respectively - each taken two offsprings with the most heavy weights. Once the offsprings were born *Rattus norvegicus* sacrificed using chloroform, weighed, taken of his brain, made preparations and colored immunohistochemical staining. BDNF expression is calculated for each sample. Compared between groups using a statistical test. Conduct a feasibility study is obtained from the Ethics Committee of the Faculty of Veterinary Medicine, Universitas Airlangga.

RESULTS AND DISCUSSION

The *Rattus norvegicus* used in the study, we noted their gestasional age and was born at the age of 19-21 days gestation.

Table 1. *Rattus norvegicus* mothers' characteristics by gestational age

Gestation age	Control		Default sequence Mozart		Reversed sequence Mozart	
	∑	%	∑	%	∑	%
19 days	2	22.2%	1	11.1%	3	33.3%
20 days	5	55,6%	6	66.7%	5	55,6%
21 days	2	22.2%	2	22.2%	1	11.1%
Total	9	100%	9	100%	9	100%

Table 1 shows the largest presentation of *Rattus norvegicus* gestational age at 20 days, 55.6% of the control group and the treatment group Mozart default sequence by 66.7% and group Mozart reverse sequence of 55.6%. *Rattus norvegicus* mothers used in the study, were selected based on weight range of 120-150 g, then we randomized to each group of 9 samples.

Table 2. *Rattus norvegicus* mothers' characteristics based on weight

Weight (grams)	Control		Default sequence Mozart		Reversed sequence Mozart	
	∑	%	∑	%	∑	%
120-130	-	-	-	-	-	-
131-140	2	22.2%	3	33.3%	4	44.4%
141-150	7	77,8%	6	66.7%	5	55,6%
Total	9	100%	9	100%	9	100%

In Table 2, we used the mains *Rattus norvegicus* with the highest weight ranges from 141-150 grams in all three groups. In the control group 141-150 gram weight of 77.8% in the control group and 66.7% of default sequence Mozart group and 55.6% in the reversed sequence Mozart. The heaviest weights has to be sacrificed and cuts on his brain. Two *Rattus norvegicus* offsprings' brain used as a preparation and staining.

Table 3. Characteristics of the *Rattus norvegicus* by weight

Weight (grams)	Control		Default sequence Mozart		Reversed sequence Mozart	
	∑	%	∑	%	∑	%
3.00 to 3.99	-	-	-	-	-	
4.00 to 4.99	2	11.11%	4	22.22%	-	
5.00 to 5.99	13	72.22%	11	61.11%	15	83.33%
6.00 to 6.99	3	16.67%	3	16.67%	3	16.67%
Total	18	100%	18	100%	18	100%

Table 3 shows the *Rattus norvegicus* offsprings' weight that we use the most weight from 5.00 to 5.99 grams for each group (control group amounted to 72.22%, the default sequence group 61.11% Mozart and Mozart group reverse sequence of 83.33%). To measure the expression of BDNF, the data of each sample rated semiquantitatively according Remmele method that has been modified. In the table below shows BDNF expression in the control and treatment groups both at the cerebrum and cerebellum.

Table 4. Characteristics of *Rattus norvegicus* offsprings based on the expression of Brain Derived Neurothropic Factor (BDNF) in the brain

Groups	The cerebrum	Cerebellum
Default Sequence	85.6	85.3
Reversed sequence	50.2	54.2
Control	61.2	46.7

Table 4 shows the expression of BDNF in the treatment group Mozart Raw sequence in the cerebrum and cerebellum higher at 85.6 and 85.3 compared to the treatment and control Mozart reverse order. In the cerebrum obtained BDNF expression was lower in the treatment Mozart reverse order compared to controls. From the results that we get, we analyzed using descriptive statistics. Table 5 shows the average weight of *Rattus norvegicus* mothers and offsprings in each group.

Table 5. The average weight holding *Rattus norvegicus* and *Rattus norvegicus* offsprings' weight in the control group and the treatment

Group	Mothers' Body Weight (g)	Offsprings' Body Weight (grams)
	mean ± S/D	mean ± S/D
Control	144.89 ± 5.84	5.46± 0.43
Mozart Default	141.89 ± 4.62	5.54± 0.52
Mozart Reversed	142.11 ± 6.56	5.53± 0.38

To find out whether our study sample normal distribution or not, from the table above, we do a first test for normality using the Kolmogorov-Smirnov test.

Table 6. Kolmogorov-Smirnov normality test on *Rattus norvegicus* mothers and offsprings weight

Weight (grams)		Kolmogorov-Smirnov		
		Statistics	Df	p
Mothers	Default sequence	0.183	9	.200
	Reversed sequence	0.226	9	.200
	Control	0.204	9	.200
Offs-prings	Default sequence	.180	18	0.126
	Reversed sequence	0.134	18	.200
	Control	0.188	18	0.094

Based on the Kolmogorov-Smirnov test showed p> 0.05, which means that the weight on the mothers and offsprings of *Rattus norvegicus* normal distribution.

Analysis of research in cerebrum

Kolmogorov-Smirnov test done first as a test of normality for BDNF expression in each group. Then analyzed with descriptive statistics such as in the table below. On normality test results obtained when p>0.05 in all three groups showed normal data distribution. Normality test results BDNF expression in the cerebrum showed normal distribution of the data (p>0.05) and we use ANOVA test and Post Hoc.

Table 7. Kolmogorov-Smirnov test for normality in BDNF expression in the cerebrum

BDNF	p
Default sequnce	.200
Reversed sequence	0.065
Control	0,062

Table 8. The average and standard deviations of BDNF expression in the cerebrum

Default Sequence mean ± SD	Reversed sequence mean ± SD	Control group mean ± SD
8.98 ± 1.31	5.58 ± 3.08	6.80 ± 1.95

Table 8 shows the average expression of BDNF in the cerebrum. Data with normal distribution in BDNF average values obtained were highest in the group of default sequence Mozart group when compared to reversed sequenced Mozart group and the control group. Table 9 shows the results of ANOVA test on BDNF expression cerebrum 0.04 p value (<0.05) showed that BDNF expression is obtained a significant difference between the default sequence Mozart, Reversed sequence Mozart and control.

Table 9. Anova test on the expression of BDNF cerebrum

Group	BDNF (Mean)	The p-value
Between groups	36.473	0.004
In Group	5.149	

Table 10. Post Hoc LSD test results BDNF expression Mozart group of raw sequence, in reverse order and control in the cerebrum

Groups	Groups	The p-value
Default sequence	Reversed sequence	0.001
	Control	0.018
Reversed sequence	Default sequence	0.001
	Control	.264
Control	Default sequence	0.018
	Reversed sequence	.264

Table 10 shows the test results Post Hoc LSD cerebrum BDNF expression in default sequence Mozart group, reverse sequence Mozart group and control the distribution of normal data. Analysis of the default sequence Mozart group and reverse sequence Mozart group shows the p value=0.001 (<0.05), which means that BDNF expression obtained significant differences in these groups. Analysis of the default sequence Mozart group and control shows the p value=0.018 (<0.05), which means obtained significant differences BDNF expression in the default sequence Mozart group and the control group. For a comparison between the control group and the reversed sequence Mozart p value=0.264 (>0.005) showed no significant difference.

Analysis of research in Cerebellum

As in the cerebrum, cerebellum results data we Kolmogorov-Smirnov test done first as a test of normality for BDNF expression in each group. Then analyzed with descriptive statistics such as in Table 11.

Table 11. Kolmogorov-Smirnov test for normality in BDNF expression in the cerebellum

BDNF	p
Default sequence	.200
Reversed sequence	0.096
Control	.200

On normality test results obtained when p>0.05 in all three groups showed normal data distribution. Normality test results BDNF expression in the cerebellum showed normal distribution of the data (p>0.05) and we use Anova.

Table 12. The average and standard deviations of BDNF expression in the cerebellum

Default sequence mean ± SD	Reversed sequence mean ± SD	Control group mean ± SD
9.48 ± 1.41	6.02 ± 3.25	7.14 ± 2.54

Table 12 shows the average BDNF expression in the cerebellum. Data with normal distribution in BDNF average values obtained were highest in the default sequence Mozart group.

Table 13. Anova test on the expression of BDNF cerebellum

Group	BDNF (Mean)	The p-value
Between groups	46.55	0.003
In Group	6.34	

Table 13 shows the test results on the expression of BDNF cerebellum ANOVA p value of 0.03 (<0.05) showed that BDNF expression is obtained a significant difference between default sequence Mozart, reversed sequence Mozart and control.

Table 14. Post Hoc LSD test results BDNF expression on default sequence Mozart group, reversed sequence Mozart group and control in the cerebellum

Groups	Groups	value P
Default sequence	Reversed sequence	0.008
	Control	0.001
Reversed sequence	Default sequence	0.008
	Control	.490
Control	Default sequence	0.001
	Reversed sequence	.490

The above table shows the analysis of the default sequence Mozart group and control shows the p value=0.001 (<0.05), which means obtained significant differences BDNF expression. Analysis of the default sequence Mozart group and reverse sequence shows the p value=0.008 (<0.05), which means obtained significant differences BDNF expression. For comparesons between groups reversed sequence group and control p value=0.490 (>0.05) showed no significant difference.

This study was conducted to compare the expression Brain Derived Neurothropic Factor (BDNF) against exposure to default sequence Mozart, reversed sequence Mozart and without exposure for an hour during the night that everything was done since the 10th day of gestation. This is to prove that sequence of songs also have an important point in giving exposure to Mozart.

Hermanto (2002) in his research said that Mozart during pregnancy increases the number of brain cells of mice better than the group of gamelan music, dangdut and control (without exposure).[13] Suryanti (2009) in his research on humans say that serum BDNF levels obtained newborns was significantly higher with exposure to Mozart than without exposure to Mozart's music.[13] Widyanto (2013) also examined in humans and the results obtained comparison of serum BDNF levels of infant cord blood DHA treatment group and Mozart composition is higher compared to the DHA treatment group.[14] Marzban (2011) in his research said that the BDNF levels in the hippocampus of newborn rats that get exposure to Mozart's music improved significantly when compared with no exposure.[15] Research conducted Xing (2015) showed that while Mozart K.448 have positive effects on cognition, but Mozart version of retrograde (backwards) have a negative effect on the performance of rats. Until now we have not found any research on Mozart given in reverse order.[16]

This research was conducted with the design of randomized post test only control group design to achieve optimum results, carried out the closure of the glass object code for each counting brain cells and BDNF expression. The new code was opened after the inspection is completed so that inspectors and investigators do not know the results of the previous inspection.

In this study, all of the pregnant *Rattus norvegicus* gave birth on 19-21 days gestation. No *Rattus norvegicus* experienced preterm birth, miscarriage and death. *Rattus norvegicus'* newborn offsprings were sacrificed. This was done to reduce weight bias. Furthermore, *Rattus norvegicus* had newborn two newborn offsprings, from which the heaviest were immediately sacrificed by means of decapitation. Selected heaviest weight because previous research has found that the heavier weight, the less apoptosis that occurs. Furthermore, the homogeneity of *Rattus norvegicus* mothers and offsprings' body weight were tested beforehand with the Kolmogorov-Smirnov normality test, showing that both had normal distribution.

This study was conducted 10 days since pregnancy *Rattus norvegicus* due to the formation of the *Rattus norvegicus* perfect hearing function at the age of 9-10 days gestation. Ernawati (2008) using the apoptotic index to assess the influence of Mozart's music at the beginning of pregnancy when compared with gestational age of 10 days were not significantly different. This is possible because the stimulus in the form of sound waves received through the ear, then the mechanical wave is converted into electrical impulses and transmitted via the auditory nerve cortex when the ear is fully formed. Thereby giving the musical stimuli will begin to take effect after the form and functioning of the ear and begin the formation of synapses, ie at 20-24 weeks of gestation or the equivalent of gestation days – 10 in mice.[16]

From some research on Mozart, research conducted by Marzban (2011) that the BDNF levels in the hippocampus of newborn rats that get exposure to Mozart's music improved significantly when compared with no exposure.[15] It is also consistent with the results of research conducted by Fran Rauscher and Hong et al, in a study conducted on mice given a stimulus to Mozart than rats given a stimulus noise, showed mice given a stimulus to Mozart smarter than mice given stimulus noise. After examination of the mice turned out showed increased expression of BDNF, CREB, and synapsin I in mice given a stimulus to Mozart than control mice.[17]

From the characteristics of the research we did on the cerebrum and cerebellum obtained Neurothropic expression of Brain Derived Neutothropic Factor (BDNF) was highest in the default sequence Mozart group when compared to reversed sequence Mozart group order and control. BDNF expressions in Mozart reversed sequence Mozart group have lower value compared to the control. In the cerebrum obtained an average expression of BDNF in default sequence Mozart group 8.98, in reversed sequence Mozart group 5.58 and 6.80 in controls, whereas in the cerebellum obtained an average expression of BDNF 9.48, in reverse order Mozart 6.02 and on controls 7.[18]

From statistical calculation Anova test showed a significant difference in the value of the three groups of BDNF expression in both the cerebrum and cerebellum is the cerebrum p-value 0.004 and p-value 0.003 cerebellum. In the analysis of Post Hoc LSD cerebrum and cerebellum obtained significant value of the comparison default sequence Mozart group compared to the reversed sequence Mozart group (cerebrum $p=0.001$ and cerebellum $p=0.008$) and significant difference between default sequence Mozart group and control (cerebrum $p=0.018$ and cerebellum $p=0.001$). Thus can we prove that the exposure of Mozart, the order of the songs have an important role in increasing the expression of BDNF.

If we search from multiple review of the literature, from the theory put forward by Petacchi (2005) that the cerebellum has a response to auditory stimulation as the cerebrum on inspection Positron Emission Tomography (PET) and Functional Magnetic Resonance Imaging (fMRI).[19] Another theory says that the increase in BDNF may increase the plasticity of nerve cells in cerebellum. Sidon and Musiek said a theory that the stimulation of the auditory pathways to the cerebellum via two pathways, namely pathways directly and indirectly. Direct pathway, cerebellum receive auditory information from the nucleus projection cochlearis. In the indirect pathway, the signal to the auditory stimulation derived from the primary auditory cortex, medial geniculate body, and inferior colliculus to the pontine nucleus and to cerebellum. This is what makes the value of BDNF expression in the cerebellum default sequence Mozart increase as in the cerebrum increased.

CONCLUSIONS

There were significant differences of the expression of Brain Derived Neurothropic Factor (BDNF) between the exposure to default sequence of Mozart music, of the reverse sequence and control in the cerebrum and cerebellum of newborn *Rattus norvegicus*. BDNF expression in the cerebrum and cerebellum of newborn *Rattus norvegicus* exposed to default sequence of Mozart music group was significantly higher than that in reversed sequence group and that in control group. There were no significant differences in the expression of BDNF *Rattus norvegicus* cerebrum and cerebellum of newborn between receiving exposure to reversed sequence Mozart group and control.

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