

**REVIEW ARTICLE :****The evidence for the influence of musical compositions during pregnancy to the structure and functions of the offsprings' brain****Hermanto Tri Joewono**

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**ABSTRACT**

**Objective:** to compile studies in Surabaya on the effect of Mozart compositions during pregnancy on the number of the offsprings brain neuron, glia, BDNF, apoptotic neurons and, neuronal dendritic density. These series of studies aimed to develop environmental-enrichment model during pregnancy so we can have better brain for the next generation. Better brain means better capacity in processing information, solving the problems, and creating new solutions that depends on the number of neuron, glia, ratio glia/ neuron and synapses. We do believe in the motto of "From Neurons to Nation"

**Overview:** There were 38 studies, in animal models except two in human subjects, all of them with control, prospective, and randomized. The first group consist of analyze the frequency, sequence, time, duration, gestational age, distant, and intensity of Mozart composition. The second group: try to analyze the mechanism and compare with variety of other compositions including other western music(Chopin, Beethoven, Blues, Jazz, Rock) and Indonesian music(Gamelan Jawa, Sunda, Bali, Pop, Religious). The third group: combine with nutrition, reverse sequence, involving cerebrum and cerebellum, and right-left hemisphere. There were no growth restricted, dead, and malformed offsprings in both groups. The BDNF expression, synapsin I expression, the number of neuron, number of glia, and dendritic density of the exposed groups were higher than control. The neuronal apoptotic index were lower in the exposed groups

**Conclusions:** Mozart compositions during pregnancy increased the BDNF, synapsin I, number of neuron, number of glia, dendritic density and, also decreased the neuronal apoptosis in offsprings' brain

**Keywords:** pregnancy; Mozart compositions; newborn/ offsprings' neuron; glia; BDNF

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**ABSTRAK**

**Tujuan:** mereviu seluruh penelitian mengenai pengaruh kombinasi komposisi Mozart dan nutrisi selama hamil terhadap neuron glia, BDNF, synapsin, indeks apoptosis otak hewan coba baru lahir. Rangkaian penelitian ini ditujukan untuk mengembangkan model pengkayaan lingkungan selama hamil sehingga dapat diperoleh generasi mendatang dengan otak yang mempunyai kapasitas yang lebih baik dalam memproses informasi, menyelesaikan masalah dan menciptakan solusi baru; yang sangat tergantung jumlah neuron, glia, rasio glia/ neuron dan pertumbuhan sinaps. Kita percaya dengan moto *From Neurons to Nations*.

**Rangkuman:** terdapat 38 penelitian pada hewan coba dan 2 pada manusia, semuanya dengan kontrol, prospektif dan acak. Kelompok pertama terdiri dari penelitian mengenai frekuensi, intensitas, urutan, jarak dan intensitas lagu; kelompok kedua: mencoba menganalisa mekanismenya dan membandingkan dengan berbagai komposisi lain termasuk musik Barat(Chopin, Beethoven, Blues, Jazz dan Rock) dan musik Indonesia(Gamelan Jawa, Sunda, Bali, Pop dan Religi). Kelompok ketiga mengkombinasikan dengan nutrisi, membalik urutan lagu, membandingkan otak besar dan otak kecil serta otak kanan dan kiri. Pada semua kajian, tidak didapatkan kematian, pertumbuhan janin terhambat, cacat bawaan pada kedua kelompok. Jumlah neuron, glia, kepadatan dendrit, ekspresi BDNF synapsin I secara konsisten lebih tinggi pada kelompok perlakuan. Indeks apoptosis neuron juga lebih rendah

**Simpulan:** dari puluhan kajian yang sudah dilakukan, komposisi Mozart selama hamil meningkatkan ekspresi BDNF dan synapsin I, jumlah neuron, glia, dan kepadatan dendrit dan menurunkan indeks apoptosis neuron

**Kata kunci:** Kehamilan; komposisi Mozart; bayi baru lahir; neuron; glia; BDNF

## What's new

We compile our studies on the influence of environment enrichment (the combination of nutrition and Mozart compositions) during pregnancy to the number of offsprings' brain neurons, glia, BDNF, Synapsin I, Apoptotic Index). The focus is not only the disease but also mal fetal brain growth and development.

## Impact

Fetal brain growth and development, structure and markers for brain growth, change the insult during pregnancy to environmental enrichment, fulfillment of fetal rights and, more holistic approach to obstetrics/fetal medicine issues are proposed to be new subjects of Obstetrics/MFM.

It is the right of the unborn child - as the future owner, to have better brain: better biopsychosocial capacity to process information, to solve the problem, and create something new. The forgotten in utero brain growth and development-especially synaptogenesis and neuronal apoptosis, allow obstetricians to have the opportunity and privilege to fulfill this right. We will deal not only with the prevention, prediction and management of maternal, and fetal diseases but also with human brain growth and development. Combination of certain nutrition and musical stimulation during pregnancy could be part of more holistic antenatal care in the future

## INTRODUCTION

Indonesian Human Development Index (a summary measure for assessing long-term progress in three basic dimensions of human development: a long and healthy life, access to knowledge and a decent standard of living) is the lowest in Southeast Asia regions. Indonesia's HDI value for 2018 is 0.707 — which put the country in the high human development category — positioning it at 111 out of 189 countries and territories.<sup>1</sup> Education had successfully improved the index in many countries which needs one of the things is quality of the brain.<sup>1</sup> One of the capacities the brain is 9 biopsychosocial potential or intelligences – name after Gardner which based on 8 criterias<sup>1</sup> and, related with the brain structure.<sup>1</sup> Diamond found the different structure of Einstein's brain compared with the other men's brains.<sup>1</sup> It is already recognized that the main process of growth and development of the fetal brain involves neuronal and, glial cell proliferation, migration, differentiation, myelination, apoptosis, and synaptogenesis.<sup>1</sup>

These processes depend on nutrition, stimulation, and genetic inheritance or nature and nurture conditions – insults will result fetal programming of adult health and diseases including brain region,<sup>13-20</sup> environment enrichment results in better brain structure, and functions especially the apoptosis, and synaptogenesis<sup>1</sup> Mistretta & Bradley, Tomatis, Campbell, Logan, Rauscher, Bodner etc, elaborate these findings with auditory stimulation during pregnancy especially composed by Mozart in laboratory, and clinical settings.<sup>1</sup> Connecting these findings we developed model and conceptual framework on research and done by some group of researchers in biomolecular and, clinical levels mostly on musical stimulation during pregnancy and, combined it with research on nutrition and stress during pregnancy, and birth (Fig 1)<sup>1</sup>

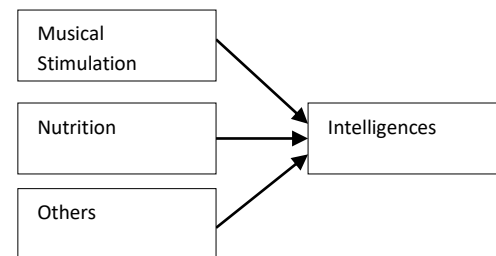


Figure 1. Model describing the relationship between nature (stimulation and nutrition) and nature(others including genetic, habits, disease) in Developing Intelligences.

Intelligences start to be developed in the womb, depend on number of neurons, glia and synaps which inturn depend on the stimulation, nutrition and other condition such as genetic, disease, habits etc. This mini-review tries to compile those studies in Surabaya on the effect of Mozart compositions during pregnancy to the number of the offsprings' neuron and glia cells, brain BDNF, apoptotic neurons and, neuronal dendritic density. Hopefully, this article provides the evidence for the efficacy of Mozart compositions during pregnancy to the offsprings' brain structure and function.

## Overview

We analyze all the studies that had been done in Surabaya in the last 18 years that correlated the variable Mozart during pregnancy and newborn or offsprings BDNF, number of neuron and glia, dendritic density, and apoptotic index.

From Group I studies, we developed sequence of 14 Mozart compositions, intensity (65 dB – maximal

loudness), distant (in the mother's belly/abdominally), timing (only at night), duration (60 minutes), and gestational age 20 weeks of pregnancy. Although each study only in small numbers of animal models, all of the studies showed consistently the positive effects of musical stimulation during pregnancy to the cerebrum - and then to the cerebellum also, of the offsprings' brain. Since the year 2000, we started the studies by choosing the right sequence based on frequency analysis, that was confirmed in the year 2019 with professional music production house, which consistently give sinusoidal pattern in one composition, in ordered sequence and in 1000 x zooming frequency analysis, high proportions of major keys and played by orchestra. Then, measuring the best distance between loudspeaker and fetus<sup>1</sup>, analyze the influence to the fetal biophysical profile<sup>1</sup>, fetal heart rate response in day and night<sup>1</sup>, started measuring BDNF in animal model<sup>1</sup>, Ismudi study, compared that default sequence with Thomas Verny: Love Chords and Don Campbell: Music for Moms and Moms-to-be CDs and measuring the neuronal apoptotic index<sup>1</sup>, and the gestational age<sup>1</sup>. Duration of exposure by Rino and his team<sup>1</sup>, and again day and night but in animal model.<sup>1</sup>

Results of the first group were 1. Mozart gave the best result 2. Sequence is important 3. In 60 minutes – 14 compositions 4. Start at 20 weeks of gestational age 4. In the night 5. The loudspeaker must be in mother's belly 6. combined with the nutrition the musical stimulation.

Of note, we have some differences with other researchers that we use Mozart compositions but NOT THE SAME what the Western society called Mozart effect as follow: it is exposed to the pregnant mother but intended for the unborn child, place the headset on mothers' belly, not mothers' ears, consisted 14 compositions in fixed order – not only one K448, time: in the night only, duration: 60 minutes and start at the 20 weeks of pregnancy. All of the studies had been summarized in reference no 1 – a book in bahasa Indonesia that was published in 2012. The following table is the 14 compilations that had been chosen among 626 Mozart compositions.

From Group 2, and Group 3, we tried to reveal the mechanism of musical exposure at molecular level by measuring the BDNF, Synapsin 1, MTORC1<sup>2-5</sup> at cellular level and compare Mozart compositions with other Western compositions Beethoven and Chopin compositions<sup>6-9</sup> Jazz, Blues and Rock compilations<sup>10-11</sup>, and Indonesian compositions Indonesian traditional Gamelan<sup>12-16</sup>, with Indonesian Pop and Religious<sup>17-20</sup> music. We continued with reversed sequence,<sup>21-24</sup> and

combined it with food restriction.<sup>25-28</sup> Compared with Chopin and Beethoven, Mozart composition gave higher neuron, dendritic density and lower neuronal apoptotic index. The same results, found with Jazz, Blues, Rock compositions, and also with Indonesian music including traditional Gamelan, Pop and religious compositions

Table 1. The sequence of Mozart composition (in order)

No	Title
1.	K 265 Twinkle Twinkle Little Stars
2.	K 525 Eine Kleine Nacht Musik
3.	K 467 Piano Concerto In C Major
4.	K 545 Piano Sonata No 16 In C Major
5.	K 331 Piano Sonata In A Major
6.	K 284 Sonata In D Major
7.	K 492 The Marriage Of Figaro
8.	K 158 Andante In G Minor
9.	K 137 Andante In B Flat Major
10.	K 527 La Ci Darem La Mano, Allegro-From Don Giovanni
11.	K 63 Adagio, V, From The Cessation In G Major
12.	K 131 Symphony No 25 G Major
13.	K 142 German Dance In C Major
14.	K 153 Symphony No 41 C Major

## DISCUSSION

These studies also confirmed the Fetal Origins of Adult Disease – Developmental Origins of Health and Disease: hypothesis developed by Barker, Gluckman, and Hanson. The different is the insult in their hypothesis is changed into environmental enrichment during pregnancy<sup>1</sup> Even this issue is still controversial and the mechanism underlying the effects is not completely understood, many researchers had conducted studies in the last decades.

Compared with other studies, these studies confirmed the influence of musical exposure during pregnancy to the BDNF and neuronal apoptosis of the offsprings' brain as in Table 2.

## Mechanism

Pregnancy as window of opportunity to optimalise brain growth and development has been accepted by many experts. Rice & Baron<sup>40</sup> stated that vulnerable periods during the development of the nervous system proliferation, migration, differentiation, synaptogenesis, myelination, and apoptosis are sensitive to environmental insults. Some of them extend from the embryonic period through adolescence.

Table 2. Comparisons with other studies<sup>1, 29-39</sup>

Writer	Results
Thomas Verny	"Nurturing the Unborn Child" - Womb harmonics: nothing gives a child a more solid foundation in life than the experience of being loved and wanted in the womb
Beatriz Manrique	About 75% of the nervous system maturity is genetically programmed, the rest depends on experiences, providing an enriched environment, to promote better bio-psychological-social development
Brent Logan	BabyPlus method reduce the fetal neuronal apoptosis, results in better milestone scale achievement
Rene van de Carr	There is a critical time in an infant's development beginning at about five months into pregnancy. Interaction between the baby and its environment stimulates brain growth both before and after birth
Angeluci <i>et al</i>	Music exposure significantly enhanced BDNF levels, and decreased NGF in hypothalamic levels
Marzban <i>et al</i>	Rats exposed to Mozart Sonata music had significantly increased BDNF content in the hippocampus as compared to control rats
Chaudhury S <i>et al</i>	Auditory stimulation triggers the BDNF-Trk pathway, which is similar to the pathway stimulated by enriched environment.
Chikahisa <i>et al</i>	Music-exposed mice completed a maze learning task with fewer errors, lower levels of BDNF and higher levels of TrkB and PDK1 in the cortex.
Kim <i>et al</i>	Exposure to music during pregnancy increased neurogenesis in the motor and somatosensory cortex of rat pups
Sanyal <i>et al</i>	Unpatterned noise stimulated group showed an attenuated volume, reduction in the total neuron number, mean neuronal nuclear area was significantly reduced
Partanen <i>et al</i>	Our results show that extensive prenatal exposure to a melody induces neural representations that last for several months
Xing <i>et al</i>	the retrograde version has a negative effect on rats' and human performance, rhythm is a crucial element in producing the behaviour effects

How brain percept and process music have been debated for years, including how the fetal brain reduce apoptotic process are not completely understood. Griffith<sup>41</sup> and Tramo *et al*<sup>42</sup> and also Lecanuet *et al*<sup>43</sup> explained some part of the process – but there many unanswered questions. These series of studies showed that the sequence of Mozart increase BDNF, Synapsin 1, reduce neuronal apoptotic index, and increase number of neurons, glia and dendritic density. More extensive explanation but inconclusive discussion presented by Lai<sup>44</sup>, Arabin<sup>45</sup>, and Partanen *et al*.<sup>46</sup>

### Learning from music as medicine

There are many studies on usage of music as complementary medicine especially in neurological disease including stroke, disorders of consciousness, seizure – epilepsy that showed positive results. There was also better improvement in patients with coronary artery bypass. The question is, if musical exposure is functioning in pathological conditions, could also be applied in physiologic conditions? This question also make us use “stimulation” term not “therapy” because we use it for healthy fetus.<sup>47-55</sup>

### Domain of the issues

These issues(intelligence/s, fetal brain growth, and development, environmental enrichment) are not the mainstream in medical institutions such as WHO, FIGO, ACOG, SMFM, UNICEF, textbooks, and journals for Obstetricians, Maternal-Fetal Medicine Subspecialist such as Williams Obstetrics, Creasy and

Resnik's Maternal-Fetal Medicine, Fetal Medicine. The psychologist, neuroscientist, and pediatricians address these issues, reflecting the division of mind, and body; care of illness versus disease; in short what we have done so far is a less holistic approach.

Real examples of this less holistic approach in obstetrics are 1. Preconceptional counseling: only to identify and modify risk factors 2. antenatal care: positive experience, ultrasonography assessment: only to confirm gestational age, find congenital malformation, fetal wellbeing and, adequacy of nutrition and oxygenation 3. birth: medicalization of birth; 4. neonatal care: only assessment of the physical conditions. No assessment on the pregnancy perspectives as life-changing events, longterm impact on adult health including intelligences and disease, planning(when, how many, interpregnancy interval), acceptance(unwanted pregnancy, family planning failure), bonding and attachment, fulfilling the fetal rights for optimizing their brain growth and development such as low maternal stress, and special treatment for pregnancy in outbreaks, refugees, disaster.

### Again and again: The forgotten in utero human brain growth and development

Most of the experts rely heavily on brain weight as measures of brain growth, and brain growth and development chart proposed by Shonkoff and his team<sup>55-56</sup> which show obvious differences compare with that were mentioned by Collin<sup>11</sup> and Hill.<sup>12</sup>

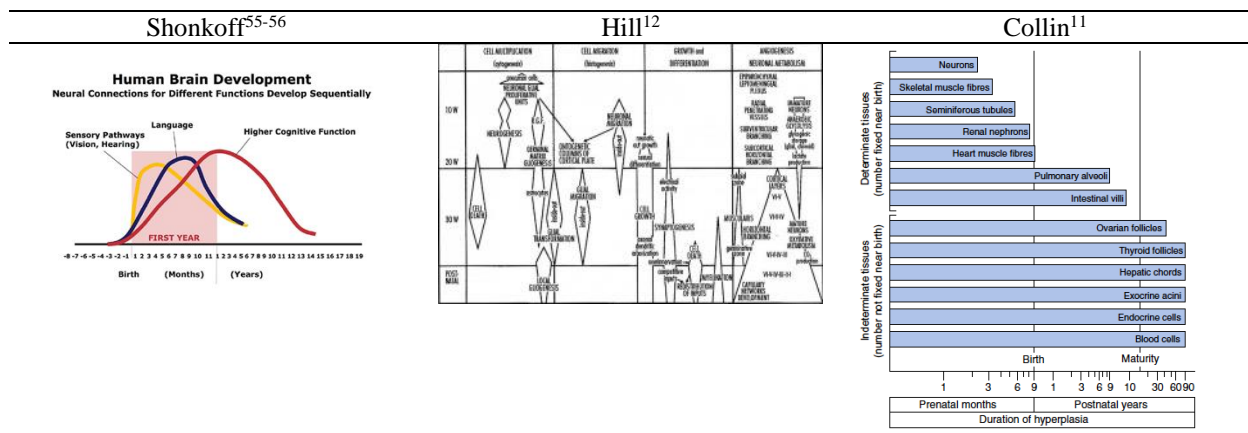


Figure 2. Shonkoff et al consider in utero brain growth and development only tiny part of brain development, on the contrary, Hill and Collin had different pictures

**CAUDA**

With these series of studies there will be new perspectives and opportunities on preparing the next better generation efforts as follows:<sup>55-62</sup>

1. Fetus is better considered as the future owner(biopsychosocial entity) not only biophysical entity that has right to fulfill
2. This kind of environmental enrichment is fulfilling one of his/ her rights
3. The womb is not a waiting room, it's a prenatal classroom and maybe one of the most important classroom in his/ her life
4. Fetal intelligences are part of health and must be included in the prenatal care - combination of musical stimulation and nutrition may be offered to prepare the fetal neuron – figure 1
5. Redefine of obstetrics as not only dealing with pregnancy, delivery and puerperium but also how to prepare the neurons of the next generation - much longer perspective. The Obstetrics will face a new era: a non-disease issue: intelligences and, the role of Obstetricians and midwives will be much important because they will deal with motto: From (fetal) Neurons to Nations
6. There are some studies needed to answer so many questions - and we realized that we are dealing with the mysteries of the most complicated thing in the universe: the fetal brain, the beauty of music and the miracle of pregnancy
7. In the developed countries the trend in music issue is to train the student skill in music - we have different approach that we expose certain sequence of music to the fetus.

8. Referring to FOAD – DOHaD hypothesis, this approach reflect the important of changing insult into environmental enrichment that make fetal adaptation much better and positive
9. In evolutionary perspective, this effort reflects different approach to survive, not with dealing/ adapt with the nature but with better brain and that in turn can have better adaptation capabilities

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