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The cerebrum and cerebellum of *Rattus norvegicus* offspring, whose mothers were exposed to a sequence of 14 Mozart compositions during pregnancy, expressed higher levels of BDNF and dendritic density, but not mTORC1

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ABSTRACT

Introduction: To investigate Brain-Derived Neurotrophic Factor levels, Mammalian Target of Rapamycin Complex 1 levels, and Dendritic Density in the cerebrum and cerebellum of *Rattus norvegicus* offspring following prenatal Mozart compositions exposure.

Material and Methods: An experimental study with a randomized post-test-only control group design was conducted at the Animal Laboratory of the Faculty of Veterinary Medicine, Universitas Airlangga, following ethical clearance. A 13 healthy pregnant female *Rattus norvegicus* were randomly chosen and exposed to 14 Mozart compositions, beginning on gestation day 10 until delivery, while another 13 served as the control group. At day 20, the rats were sacrificed, 2 offsprings' brains (the heaviest) were extracted, and BDNF levels were analyzed using the ab203573 immunohistochemistry kit, mTORC1 levels using the pSer2448 kit, and Dendritic Density using silver impregnation. Statistical analysis was performed accordingly with a significance level of $p < 0.05$.

Results: BDNF levels and Dendritic density in the cerebrum of the treatment group were higher (2.27 ± 1.41 vs. tr 7.44 ± 2.09, $p < 0.05$) and (4.42 ± 2.04 vs. 6.67 ± 1.23, $p < 0.05$). In the cerebellum, BDNF levels and Dendritic density in the treatment group were higher (1 vs. 8, $p < 0.05$) and (3.34 ± 1.94 and 7.91 ± 2.45, $p < 0.05$). mTORC1 levels in the treatment group were lower but not statistically significant in both areas.

Conclusion: Prenatal 14 Mozart compositions exposure during pregnancy increased *Rattus norvegicus* offsprings' cerebrum and cerebellum BDNF levels and Dendritic Density. A correlation was found between BDNF levels and dendritic density.

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INTRODUCTION

Hill and Shonkoff and others emphasize that pregnancy is a critical period for neuron and glia growth, impacting future cognitive and emotional health. Human brain development starts in the womb with processes such as neurogenesis, proliferation, migration, myelination, synaptogenesis, and apoptosis highlighting the importance of a supportive prenatal environment [1–11].

Prenatal environmental factors are crucial determinants of brain development and cognitive function in offspring. Among these, exposure to sound and music has emerged as a compelling area of research. Research by Diamond, Mistretta, A Tomatis, T Verny, F Rauscher, B Logan, and D Campbell underscores the impact of prenatal environmental enrichment to anatomical brain changes [12–20]. Hermanto TJ *et al.,* and others findings suggest that exposing pregnant

Rattus norvegicus to Mozart's music leads to a reduction in neuronal and glial apoptosis [21–38].

This study seeks to understand whether this neuroprotective effect is mediated through the modulation of fetal cerebrum and cerebellum BDNF levels and increased dendritic density, facilitating synaptogenesis. Furthermore, it questions the role of the mammalian target of rapamycin complex 1 (MTORC1) in this process [39–55]. By delving into these mechanisms, especially in the cerebrum and cerebellum, this research aims to shed light on the potential benefits of prenatal auditory stimulation, offering insights into the broader implications for brain development and cognitive enhancement.

This study is part of a series aimed at improving the next generation's brain, including intelligence, as a component of health. Although the World Health Organization (WHO) defines health as a state of complete physical, mental, and social well-being, especially for newborns, this definition does not explicitly mention intelligence, bonding, attachment, or acceptance of pregnancy. Nonetheless, these elements contribute to overall well-being [56]. Howard Gardner's theory of multiple intelligences and others suggest that factors like number of neuron–glia, glia/neuron ratios, and dendritic density could influence cognitive abilities [57–73]. This study is also related to Sustainable Development Goal 3: Good Health and Well-being [74].

MATERIAL AND METHODS

Study Design

This was an experimental study employing a randomized post-test-only control group design. Healthy pregnant female *Rattus norvegicus* were exposed to Mozart compositions starting from gestation day 10 until the time of delivery. Control group were exposed to daily noise level, at day 21, two groups were sacrificed, the brain extracted and prepared for Biomarker Analysis. The brain-derived neurotrophic factor (BDNF) levels in the offspring were assessed using the ab203573 immunohistochemistry kit. Levels of mammalian target of rapamycin complex 1 (mTORC1) were analyzed using the pSer2448 kit (Abcam, Massachusetts, USA). Additionally, dendritic density in the cerebrum and cerebellum of the offspring was evaluated using the silver impregnation technique with 400x magnifying microscope in 5 different areas.

Study Location

The study was conducted at the Animal Laboratory of the Veterinary Faculty, Universitas Airlangga, following ethical clearance 2015-2016.

Statistical Analysis

Data were analyzed based on their distribution. Independent t-tests were applied for normally distributed data, while Mann-Whitney U tests were used for data that did not follow a normal distribution. Correlation analyses were conducted using Pearson's test for normally distributed data and Spearman's test for non-normally distributed data. Statistical significance was set at $p < 0.05$.

RESULTS

Cerebrum

Table 1. Mother and Offspring Weights

Group	Mother weight (gram)	Offsprings weight (gram)
	Mean S/D	Mean S/d
Control	143.08±5.84	5.55 ±0.38
Intervention	142.38±5.59	5.52±0.35

The intervention had minimal impact on mother and offspring weights. Mother weights between the control and intervention groups were similar (143.08 g vs. 142.38 g) with little variation, and offspring weights were also comparable (5.55 g vs. 5.52 g) with overlapping standard deviations (Table 1).

Table 2. Mean and p-value of BDNF, mTORC1, and Dendritic Density in Cerebrum

	Control	Intervention	p-value
BDNF	2.27 ± 1.41	7.44 ± 2.09	0.000
mTORC1	6.56 ± 2.39	5.72 ± 2.63	0.40
Dendritic Density	4.42 ± 2.04	6.67 ± 1.23	0.002

Independent t-test

There is a significant increase in BDNF levels in the intervention group compared to the control group, indicating a strong effect of the intervention. mTORC1 levels are similar between groups, with no significant difference. Dendritic density is notably higher in the intervention group, suggesting a significant impact on the cerebrum. A moderate correlation was found between BDNF levels and dendritic density in the cerebrum ($p = 0.004$) (Table 2).

The graph shows a positive linear relationship between BDNF and dendritic density, with an R^2 value of 0.263, suggesting a weak to moderate correlation. While BDNF explains about 26.3% of the variance, the scattered data points and variability indicate that other factors also contribute to dendritic density, especially at lower BDNF levels and between BDNF values of 5 and 8 (Fig.1A).

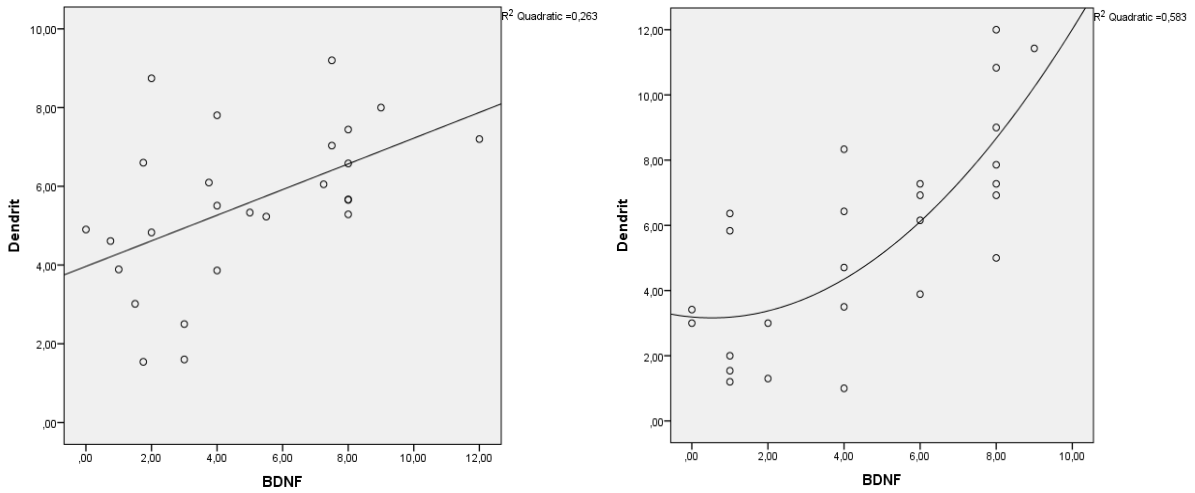


Fig. 1. A. Cerebrum: Scatter plot that shows the relationship between BDNF levels and Dendritic density: a linear regression line is fitted to the data; B. Cerebellum: The graph shows a scatter plot with a quadratic regression line fitted to the data

Table 3. Mean, Median, and p-value of BDNF, mTORC1, and Dendritic Density in Cerebellum

	Control	Intervention	p-value
BDNF	Median 1 (0-6.00)	Median 8 (4.00-9.00)	0.00*
mTORC1	Median 8 (3-12)	Median 6 (3-9)	0.40*
Dendritic density	Mean 3.34 ± 1.94	Mean 7.91 ± 2.45	0.002

*Mann-Whitney test, Independent t-test

Cerebellum

There is a significant increase in BDNF levels in the intervention group compared to the control group. The p-value of 0.00 indicates a highly significant difference, suggesting the intervention had a strong effect on BDNF expression in the cerebellum. There is no statistically significant difference in mTORC1 levels between the control and intervention groups. This suggests that the intervention did not have a notable impact on mTORC1 expression in the cerebellum. The dendritic density is significantly higher in the intervention group compared to the control group, indicating a highly significant difference. This suggests that the intervention had a positive effect on increasing dendritic density in the cerebellum (Table 3).

The quadratic regression curve fits the data well, indicating a non-linear relationship between BDNF levels and dendritic measure. The R^2 value of 0.583 suggests that 58.3% of the variance in dendritic measure can be explained by this relationship. The curve shows an initial flat or slight decrease in dendritic measure at lower BDNF levels, followed by a marked increase at higher BDNF levels. The scattered data points indicate variability, especially at mid-range BDNF values, but align with the upward trend in the quadratic fit (Fig.1B).

DISCUSSION

The study on BDNF expression in the cerebrum and cerebellum of *Rattus norvegicus* newborns with exposure to Mozart's compositions provides valuable insights into the role of BDNF in brain development. This study found that exposure to Mozart's music significantly increased BDNF expression in both the cerebrum and cerebellum compared to control groups. Fetal neuronal apoptosis (programmed cell death) during intrauterine development is a complex process influenced by various factors, mostly Brain-Derived Neurotrophic Factor (BDNF) and the mTORC1 (mammalian target of rapamycin complex 1 pathway [39–41].

BDNF is a neurotrophin that supports the survival and growth of neurons. During fetal development, BDNF is expressed in the brain and plays a crucial role in neuronal survival and differentiation. BDNF Signaling: BDNF binds to its receptors (TrkB) on the surface of neurons, activating intracellular signaling pathways that promote cell survival and growth. mTORC1 Activation: The mTORC1 pathway is a key regulator of cell growth and metabolism. BDNF signaling can activate the mTORC1 pathway, leading to increased protein synthesis and cell growth.

Neuronal Survival: Activation of the mTORC1 pathway by BDNF promotes neuronal survival by enhancing cellular processes that support growth and prevent apoptosis. Apoptosis Regulation: In the absence of sufficient BDNF or if the mTORC1 pathway is disrupted, neurons may undergo apoptosis due to the lack of survival signals. In summary, BDNF induces neuronal survival and growth by activating the mTORC1 pathway, which helps prevent apoptosis during fetal development. This sequence highlights the importance of BDNF and mTORC1 in maintaining a healthy balance of neuronal cell death and survival in the developing brain. The cerebrum and cerebellum are indispensable powerhouses of the brain, each governing distinct yet equally critical functions. An increase in Brain-Derived Neurotrophic Factor (BDNF) within these regions can have profound impacts on decision making, reasoning, and fine motor control, underscoring their significance in brain development and function.

The cerebrum, often regarded as the epicenter of cognitive prowess, is responsible for higher-order functions such as decision-making, reasoning, and problem-solving. Enhanced BDNF expression in this area fosters the growth and survival of neurons, ensuring that the intricate networks responsible for these cognitive processes remain robust and functional. This, in turn, translates to improved intellectual capabilities and a sharper ability to navigate complex life situations.

Similarly, the cerebellum, known for its role in coordinating fine motor movements, benefits immensely from increased BDNF levels. By supporting neuronal survival and synaptic plasticity, BDNF helps maintain the delicate balance and precision required for tasks ranging from intricate hand movements to maintaining posture and balance. The cerebellum's contributions to motor learning and adaptation make BDNF expression here crucial for refining motor skills and enhancing overall physical coordination. While the hippocampus and amygdala play pivotal roles in memory formation and emotional regulation, respectively, the cerebrum and cerebellum's functions are equally vital for a well-rounded, functional brain.

The hippocampus, with its association with memory, is undoubtedly important; however, without the cerebrum's capabilities in reasoning and decision-making, and the cerebellum's role in fine-tuning movements, the brain's overall efficiency would be compromised. Similarly, the amygdala's regulation of emotions is crucial, but it works in concert with the cerebrum's rationality to produce balanced responses to environmental stimuli. Thus, increased BDNF expression in the cerebrum and cerebellum is not just a matter of supporting neuronal health but also of enhancing the fundamental functions that these regions govern. It ensures that the brain's cognitive and motor capabilities are finely tuned, enabling individuals to perform complex tasks with precision and thoughtfulnes [42–50].

The potential relationship between BDNF during fetal development, particularly in the cerebrum and cerebellum, and the development of multiple intelligences as proposed by Howard Gardner maybe can also be revealed at least in part. During fetal development, the brain undergoes rapid growth and differentiation, laying the foundation for various cognitive and motor functions. Brain-derived neurotrophic Factor (BDNF) plays a pivotal role in this process, particularly in the cerebrum and cerebellum. These regions are crucial for higher-order cognitive functions, fine motor skills, and emotional regulation. Howard Gardner's theory of multiple intelligences posits that individuals possess distinct types of intelligences, such as linguistic, logical-mathematical, spatial, musical, bodily-kinesthetic, interpersonal, intrapersonal, and naturalistic intelligences.

Each of these intelligences relies on specific brain regions and neural networks. Increased BDNF expression in the cerebrum supports the development of linguistic, logical-mathematical, and spatial intelligences. The cerebrum is responsible for complex cognitive processes, including language comprehension, problem-solving, and spatial reasoning. By promoting neuronal survival and synaptic plasticity, BDNF enhances the brain's capacity to process and integrate information, fostering these intelligences. In the cerebellum, BDNF contributes to the development of bodily-kinesthetic and musical intelligences. The cerebellum is involved in coordinating fine motor movements and maintaining balance, which are essential for bodily-kinesthetic intelligence.

Additionally, the cerebellum plays a role in rhythm and timing, supporting musical intelligence. BDNF's role in promoting neuronal health and connectivity in the cerebellum helps refine these skills, allowing for more precise and coordinated movements and better musical abilities. The amygdala and hippocampus, while not the primary focus of this narrative, also benefit from BDNF's influence. The amygdala is involved in emotional regulation and interpersonal intelligence, while the hippocampus is crucial for memory and intrapersonal intelligence. BDNF supports the development and maintenance of these regions, contributing to a well-rounded cognitive profile. In short, BDNF's role in fetal brain development, particularly in the cerebrum and cerebellum, aligns with Gardner's theory of multiple intelligences. By promoting neuronal survival and synaptic plasticity, BDNF supports the development of various intelligences, enhancing the brain's capacity to process information, solve problems, and create products of value in a cultural setting [57].

The results indicate that prenatal exposure to Mozart compositions positively influences BDNF levels and dendritic architecture in offspring while also hinting at a trend in mTORC1 expression that warrants further investigation. The increase in BDNF and dendritic density in the cerebrum and cerebellum added to our understanding of the mechanisms behind this impact, which previous studies mainly addressed in other parts of the brain [21–38]. Overall, this study highlights the profound impact that prenatal auditory stimulation, particularly Mozart compositions, can have on offsprings' brain development in Rattus norvegicus, suggesting potential benefits for cognitive development [39–55].

Application to Humans:

The study on *Rattus norvegicus* suggests that prenatal exposure to Mozart compositions could enhance human fetal brain development by increasing brain-derived neurotrophic factor (BDNF) expression and dendritic density, essential for cognitive functioning. Creating enriched auditory environments during pregnancy might improve neurodevelopmental/ intelligences outcomes. However, caution is needed as human neurodevelopment is much more complex and influenced by genetic, environmental, and social factors. Further research is necessary to understand auditory stimulation's specific effects on human fetuses and long-term cognitive benefits while also considering individual differences. Integrating animal study findings with human research could help develop innovative prenatal care strategies, promoting optimal fetal brain development and better cognitive and emotional outcomes [57,58].

In the not-so-distant future, the findings on the influence of Mozart's music and BDNF on fetal brain development hold promising potential for Indonesia. As a nation striving to improve the quality of human resources, the integration of this simple and cost-effective method could be revolutionary. By incorporating environmental enrichment through music during pregnancy, we can enhance brain development from the earliest stages, laying the groundwork for improved cognitive abilities and educational outcomes. Imagine a new generation of Indonesians, nurtured from the womb with the harmonious strains of Mozart's compositions, experiencing heightened brain development.

This prenatal intervention, involving specific durations, sequences, volumes, and timings of 14 Mozart pieces, can stimulate increased BDNF expression in the cerebrum and cerebellum. As a result, these children may exhibit enhanced decision-making, reasoning, and fine motor skills, providing them with a solid foundation for lifelong learning and development. Incorporating this method into public health and education policies could democratize access to cognitive enrichment, regardless of socio-economic background. With relatively low costs and simple implementation, this approach aligns well with Indonesia's goal of fostering a more educated and capable populace. By investing in this prenatal musical enrichment, we pave the way for a future where Indonesia's human resources are well-prepared to contribute meaningfully to the nation's growth and progress. As we look forward, this breakthrough offers a glimpse into a future where educational and cognitive disparities are narrowed, and the potential of every child is maximized through early intervention. The harmonious blend of science and art in this approach not only underscores the importance of brain development but also celebrates the transformative power of music in shaping a brighter future for Indonesia [59–73].

CONCLUSION

This study contributes to the growing body of evidence supporting the notion that prenatal Mozart exposure can shape neurodevelopmental trajectories. The observed increases in BDNF and dendritic density, along with the trends in mTORC1 expression - more specifically in cerebrum and cerebellum, underscore the importance of environmental factors in shaping the developing brain. Future research should aim to further elucidate the underlying mechanisms and explore the broader implications of these findings in both animal models and human populations.

What's New

This study presents novel findings on the impact of prenatal auditory exposure on neurodevelopment in *Rattus norvegicus*. Specifically, we demonstrate for the first time that exposure to 14 sequences of Mozart compositions during pregnancy significantly increases brain-derived neurotrophic factor (BDNF) expression and dendritic density in the offspring's cerebrum and cerebellum. These enhancements are critical for neuronal survival, growth, and synaptic plasticity, suggesting that classical compositions may serve as an effective auditory stimulus for promoting positive neurodevelopmental outcomes, such as improved cognitive function and synaptic efficiency.

Impact

The study's findings highlight the significant role of prenatal auditory stimulation in neurodevelopment, showing that exposure to Mozart compositions boosts BDNF expression and dendritic density in *Rattus norvegicus* offspring. This suggests that auditory enrichment during gestation could support cognitive and brain development, informing prenatal care

practices. Additionally, the research prompts further exploration of sensory enrichment's impact on fetal development and raises questions about applying these findings to human prenatal care, particularly regarding how maternal exposure to music may affect fetal brain development and cognitive outcomes.

Strengths

One of the key strengths of this study is its systematic approach to investigating the effects of a specific auditory stimulus on neurodevelopmental outcomes. The use of well-defined parameters—BDNF expression, mTORC1 levels, and dendritic density—provides clear and quantifiable measures of brain development. Additionally, the focus on both the cerebrum and cerebellum allows for a comprehensive understanding of how prenatal exposure influences multiple brain regions. The controlled experimental design also strengthens the validity of the findings, reducing potential confounding variables.

Limitation

Despite its strengths, the study has limitations that must be acknowledged. One notable weakness is the lack of statistical significance in the increase of mTORC1 expression, which raises questions about the robustness of this finding and its implications for understanding metabolic and growth pathways in response to auditory exposure. Furthermore, the study is conducted in an animal model, which may limit the generalizability of the results to humans. The specific Mozart compositions used may also limit the scope of the findings, as different types of music could yield varying effects on neurodevelopment. Lastly, the study does not explore the long-term behavioral and cognitive outcomes of the offspring, which would provide a more comprehensive understanding of the practical implications of prenatal auditory enrichment.

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CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

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