Review

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Awareness of maternal stress, consequences for the offspring and the need for early interventions to increase stress resilience

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Abstract: Experimental and clinical studies suggest that prenatal experiences may influence health trajectories up to adulthood and high age. According to the hypothesis of developmental origins of health and disease exposure of pregnant women to stress, nutritional challenges, infection, violence, or war may “program” risks for diseases in later life. Stress and anxieties can exist or be provoked in parents after fertility treatment, after information or diagnosis of fetal abnormalities and demand simultaneous caring concepts to support the parents. In vulnerable groups, it is therefore important to increase the stress resilience to avoid harmful consequences for the growing child. “Enriched environment” defines a key paradigm to decipher how interactions between genes and environment change the structure and function of the brain. The regulation of the fetal hippocampal neurogenesis and morphology during pregnancy is one example of this complex interaction. Animal experiments have demonstrated that an enriched environment can revert consequences of stress in the offspring during critical periods of brain plasticity. Epigenetic markers of stress or wellbeing during pregnancy might even be diagnosed by fragments of placental DNA in the maternal circulation that show characteristic methylation patterns. The development of fetal senses further illustrates how external stimulation may impact individual preferences. Here, we therefore not

only discuss how maternal stress influences cognitive development and resilience, but also design possibilities of non-invasive interventions for both mothers and children summarized and evaluated in the light of their potential to improve the health of future generations.

Keywords: creative interventions to support stress resilience; fetal programming; maternal stress; prevention of psychiatric diseases.

Introduction

Aristotle already mentioned that our sensory development starts antenatally to be prepared for the challenges of extrauterine life. He postulated epigenetic processes and compared the influence of the mother’s environment with how the earth supports the development of plants [1]. Therefore, in ancient times it was recommended that pregnant women should live in a stimulating environment and avoid harmful influences.

It was not until the 20th century that new biophysical tools allowed to directly approach the fetus and to observe early fetal reactions towards maternal and external stimuli. As a pioneer, Prechtl described the continuous development from prenatal to postnatal life [2]. The care of pregnant women became a matter of public health concerns with regular controls of pregnant women; it was then that maternal-fetal medicine became a subspecialty of its own. Epigenetic studies of fetal programming such as proposed by the concept of developmental origins of health and disease (DOHaD) have demonstrated a harmful impact of maternal undernutrition on cardiovascular, metabolic, and mental health in the offspring up to adulthood [3–5]. It was recognized that not only prenatal or early postnatal exposure to undernutrition, but also maternal stress may reprogram brain development and increase risk of behavioral and neurological disorders later in life. Long-term follow up of humans whose mothers had been tested positive for maternal stress, anxiety, or depression even

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from the first trimester onwards demonstrated delayed cognitive development and impaired mental health in later life [6].

Unfortunately, pregnancy assessments usually do not involve screening tools for maternal stress, anxiety depression, although validated questionnaires such as the perceived stress scale (PSS), the stress trait anxiety inventory (STAI) or the Edinburgh postnatal depression scale (EPDS) readily exist and could be easily implemented. Maternal-fetal specialists have rather concentrated on the detection of risks of chromosomal abnormalities, fetal abnormalities pregnancy complications, or emergencies and sometimes even induce maternal stress instead of recognizing their chances to prevent the fatal consequences on the fetus up to adult life. The fetal brain seems to be a sensitive target for maternal stress effects because the differentiation of major brain structures occurs during prenatal life [7]. It is speculated that 17% of the variance of later psychological disease in adulthood are caused prenatally [8]. In pregnancies after artificial reproductive techniques, with chromosomal abnormalities or congenital heart defects (CHD), when pregnant women are exposed to natural disasters, the COVID-19 pandemic, social deprivation, violence, or war, maternal stress levels are even more increased and therefore initiate a vicious circle for the offspring [9–12] (Figure 1).

Interventions that counteract the transgenerational transmission of stress have not yet been developed although they would be desperately needed mainly in identified focus groups. Work in animal models has proven that the effects of artificially induced transgenerational maternal stress can be

“reversed” by increasing stress resilience. Many of these interventions follow the model of “environmental enrichment” (EE) and have been developed in rats and mice [13]. In this review we summarize experimental and clinical findings related to transgenerational stress, sensory and cognitive development and discuss their relevance for future pregnancy care.

Stress factors of pregnancy and fetal programming

Maternal well-being determines fetal and postnatal cognitive and psychosocial development. Numerous clinical studies have summarized the consequences of high anxiety and stress levels in pregnant women on the mental health of their offspring, but unfortunately did not translate into screening or care concepts [6, 14–17]. Meanwhile, only one European region has introduced a screening concept for maternal stress and the risks for the offspring [18]. Recent epigenetic studies have shown that early deviations in temperament and cognitive development were initial indicators of previous maternal stress. Maternal stress and anxiety or depression can persist or even increase after birth and be associated with a negative attitude towards parenthood [19]. This may have an additional impact on the offspring, which is modified by the genetic disposition or additional challenges in later life. Each stress factor can shorten the telomere length, a prominent marker of biological aging, in women by 35 base pairs [20].

Figure 1: Maternal stress measured by the perceived stress scale (PSS), anxiety measured by the stress trait anxiety inventory (STAI) or depression measured by the Edinburgh postnatal depression scale (EPDS) as it is distributed in normal pregnancies (left columns), after the diagnosis of a congenital heart defect (CHD) (centered columns) and during COVID-19 (right columns).

Modified according to ref. [10] and unpublished data from a Zoom lecture of Catherine Limperopoulos from the Center for the developing brain children's health system Washington, 2020.

During pregnancy, stress factors may increase pro-inflammatory markers and thereby even shorten telomere length in newborns [21]. It is estimated that globally, 250 million children (43%) under five years are at high risk of not reaching their physical, intellectual, and creative potential to become healthy and happy adults [14].

Acute symptoms of maternal stress are not uncommon during pregnancy and activate the “stress axis” (HPA axis) from the hypothalamus to the pituitary gland and to the adrenal cortex in both mothers and children. The fetal brain is thought to cope better with acute challenges, although in rats acute maternal stress impacted psychomotor functions in terms of motivational changes in the central-object variations of exploratory tasks in the offspring [22]. Brief maternal stress can cause sudden changes in uterine blood flow, fetal heart rate (FHR) and fetal movement patterns. The effects of stress on the HPA axis depend on age, gender, and duration of the stressor. Short-term stress also affects the HPA axis, corticosteroid levels, psychomotor function, and exploratory behavior in offspring in ref. [22].

Chronic stress can disrupt basic physiological and metabolic functions and adversely affect health. Such chronic stress situations can be simulated repeatedly over a long period of time in different generations, e.g., through social isolation. Chronic stress predisposes fetuses to changes in growth, metabolism, structure, and function of their brains and later in life even life expectancy [23–25]. Children of mothers with anxiety symptoms show a doubling of behavioral problems compared to a normal population [14]. But not only experience within a single

lifetime, but also ancestral experience affects health trajectories and chances of successful aging or disease incidence by formation of an epigenetic memory [26]. Without prevention it can take too much time for interventions of social support and sensual stimulation (“EE”) to reverse the negative consequences. Mediators are mainly cortisol, but also catecholamines, cytokines, serotonin/tryptophan, oxygen radicals, and finally the microbiome [27] (Figure 2). Epigenetic mechanisms are the link in this complex process. Biological indicators could help to identify risks and initiate early stimulation programs. Finally, even fetuses themselves are thought to stimulate the maternal sympathetic system that prepares mothers for their care through fetal movements [17].

Prenatal stress experience increases the sensitivity of the developing organism to postnatal influences [28] and explains the different outcome by a pre-existing context [29]. This may offer important opportunities for early intervention strategies.

Low birth weight also programs future mental health and was shown to be associated with hostility in later life [30]. Studies of the Dutch Hunger Winter showed that children of pregnant women who were starving during their first trimester (and certainly exposed to stress) showed increased rates of schizophrenia, depression, or inadequate stress responses in later life [31]. Since the association between birth weight and ADHD has not been confirmed in selected communities, it is likely that maternal care can break this link [32, 33]. Gestational age and birth weight explain only 1% of the variance in emotional behavioral abnormalities, but maternal stress

Figure 2: Main mediators of maternal stress via the placenta to the fetus. Modified according to ref. [14].

explains 17% mainly when the socioeconomic status is also considered [14]. Intensified maternal care can modify the outcome in groups affected by fetal growth restriction (FGR) [34]. Parental care compensates for hippocampal hypofunction in low birth weight children, thereby supporting the effective regulation of the stress axis [34]. A high socioeconomic status also reduces the effects of FGR on mental health in children [35], while a low socioeconomic status increases the negative effect of glucocorticoids and stress on long-term memory [23]. In all populations, the duration of breastfeeding promotes cognitive development even more significantly in children with FGR as compared to children with normal birth weight [36, 37].

Even chronic exposure to modern media or death of a loved one is associated with low birth weight [38, 39]. Endocrine factors such as β -human chorionic gonadotropin (β -HCG) or progesterone are possible mediators of sex-specific effects. In a multivariable regression model, an increase in maternal progesterone of 1 ng/ml in the first trimester increased girls' birth weight by 10.17 g (95% CI 2.03–18.31); in male offspring, stress during pregnancy caused growth retardation independent of progesterone concentrations [40].

The concept of environmental enrichment

The early development of animal and human offspring is determined by unchangeable (genetic) and dynamic (epigenetic) factors. From conception to old age, experiences and activities cause continuous anatomical and functional changes in our brain both in a negative and positive way. The EE paradigm was introduced by a Canadian neuropsychologist Donald Hebb in the 1940s to understand the role of experience on brain development. He compared rats under standardized laboratory conditions with rats raised like pets in his own home showing

improved memory performance [41]. Mark Rosenzweig defined EE as a combination of inanimate and/or social stimuli [13]. The experimental design has been modified in rats or mice when animals were raised in multimodal laboratory conditions that included toys, tunnels, running wheels, ladders or larger cage space (Figure 3) [42]. Thus, the animals experience a greater range of sensory, cognitive and motor stimuli compared to standard housing conditions [43]. Neuroanatomical studies in rats showed higher brain weights, stronger cross-linking of dendrites [44] and an increase in brain-derived neurotrophic factor (BDNF) expression responsible for facilitated neuroplasticity in EE [45, 46]. It was also shown that EE causes a higher degree of histone acetylation at the BDNF gene [47–49]. These mechanisms explain how EE promotes the development of the fetal brain, later counteracting premature aging, and supporting lifelong learning and stress resistance.

Animal studies can unravel the complex relationships of unfolding our genetic potential up to old age. Early experiences during developmental periods of high plasticity modify our personality. Accordingly, in pregnant mice, maternal EE accelerated cell migration in the temporal lobe [50], cell proliferation in the hippocampus [51] and earlier opening of the eyes in the offspring [52]. Neurological reflexes and motor coordination are milestones of neuromotor development [53]. Reflexes on auditory and sensorimotor stimuli developed two days earlier in the offspring of stimulated pregnant rats as compared to offspring of pregnant rats under standard conditions ($p < 0.05$). They also showed better motor functions (e.g., to bend or stand upright) up to 3 weeks after birth ($p < 0.05$).

Epigenetic mechanisms respond to environmental changes transmitting transgenerational stress by altering gene expression [54, 55]. This can occur via paternal and maternal transmission. Thus, the experience of previous generations may favor adaptations in behavior and physiology in their offspring that ensure their survival. However, stress adaptation can also harm other important

Figure 3: Schematic overview of “environmental enrichments” with variable components and social dynamics in animals. Modified according to ref. [111].

functions: Stress in male rats during spermatogenesis can cause DNA methylation passed on to the next generation (F1), leading to reduced stress reactivity and impaired motor development [56, 57]. Since exposure to stress from previous generations is irreversible and hard to control, there is considerable interest in the extent to which EE can reduce or reverse such risks. Breeding several generations in animal models can provide more feasible and practical approaches than studies in humans.

Recently developed animal models can distinguish between stress in only one preceding generation (“trans-generational”) or cumulative stress (“multigenerational”) in several preceding generations [58, 59]. In experimental designs, the effects on the offspring of both situations can then be compared with those of control groups that grew up with and without EE. It has been shown that repeated or cumulative stress can lead to limited stress resilience or adaptation at the expense of premature biological aging with a high risk of chronic disease [60, 61]. Overall, psychosocial and/or physical stress of varying duration and the EE interventions (e.g. stimulation of motor skills with or without social factors) may differ within the models [60]. An example of effective therapy with EE is the study of neuromotor function of the offspring in rat models after different stress of previous generations [58]. Animals were observed walking over a ladder (Figure 4). With increasing ancestral stress, the number of unsuccessful attempts by front or hind legs to reach the ladder rungs increased. The results were reversed after EE, so that the animals with originally high risk performed better than animals from the control group with EE (Figure 4 right). Interestingly, female

animals react more positively to social EE components by the release of oxytocin which serves as a “cuddle hormone” supporting bonding and social contacts. It also has a stress-reducing effect, increases BDNF expression and reduces aging processes [62]. The studies suggest that social networks or creative interventions can promote neuro-development into adulthood.

Sensory development and previous intervention models

The fetus not only responds to maternal stress or well-being, the increasing integrity of the sensory system allows to become aware of an outside world, whereby stimuli are first projected to subcortical areas and associated with behavioral patterns via neurons [63].

Already in the sixth week of pregnancy (SSW) skin receptors develop in the mouth region and are found on the entire skin surface until the 20th week of pregnancy. In 1952, Hooker described reactions to touch after therapeutic abortions at the end of the first trimester [64]. By this time, synapses develop in the posterior horn of the spinal cord, into which the nerve endings lead. Between 20 and 24 weeks of gestation, switch points and fibers from the thalamus to the cerebrum are formed, which are prerequisite for the experience of touch and pain [65]. Fetuses react to pain stimuli during invasive procedures [66]. After surgery on the fetus itself, a 590% increase in β -endorphin and an 183% increase in cortisol was measured; the

Figure 4: Rat crossing the ladder, mean number of wrong attempts of the rear extremities as compared to the total number of steps without (red) and with (yellow) EE.

*Significance of EE $p < 0.05$. Values represent mean value $\pm$ SD, according to ref. [53].

increase in norepinephrine was associated with the duration of the procedure [67]. Reactions to the touch of a co-twin were observed from 8 to 10 gestational weeks onwards in mono-amniotic twin gestations. Before 16 SSW, male fetuses showed faster but less complex reactions than female or mixed couples [68], suggesting early influences of testosterone [69]. Somatosensory evoked potentials were described in preterm infants from 28 weeks onwards pre-requisite for the memory of sensory sensations [70, 71]. Pre- and postnatal experiences are not necessarily comparable. Haptonomy where parents are introduced to contact their children prenatally by touch has never poorly evaluated. However postnatally premature babies have lower rates of infection and mortality when the kangaroo procedure was applied which also promoted breastfeeding rates and skull growth [72].

The outer ear is visible from the 10 gestational weeks onwards. Bones of the middle ear have already the same size as in adulthood at 18 weeks. The organ of Corti in the inner ear starts to develop at 10 gestational weeks and contains sensory and supporting cells including inner and outer hair cells with synapto- and ciliogenesis. At around 20 weeks, the morphology corresponds to the onset of cochlear function [60]. Cells of the auditory nerve enter the brainstem and pass eight synapses before entering the cerebrum. Many auditory abilities are attributable to subcortical processing.

The intrauterine world is determined by frequencies <500 Hz and sound intensities from vascular pulsations, maternal respiration, or digestion (imprinting effect) of up to 90 dB. Music and voices are audible at a volume of 8–12 dB, with male voices at 125 Hz at 125 Hz at 125 Hz being less absorbent and female voices at around 220 Hz more distinguishable. When fetuses were exposed to sounds from 100 to 3,000 Hz, initial reactions were seen at 22 weeks and 500 Hz, at 27 weeks and 100–500 Hz, and from 31 weeks on at 1,000–3,000 Hz [73]. They can also be detected by changes in electric potentials to acoustic stimuli or stimulus-related neuromagnetic fields with decreasing latency of 300–150 ms from 34 weeks of gestation to term [74].

Short behavioral responses in terms of the fetal heart rate (FHR), fetal movements or eye blinking can be observed by ultrasound. Reactions are modified by fetal behavioral stages [75]. Repeated exposure to sound has been associated with fetal conditioning: Experiments in “habituation” show that the fetus can remember and compare sounds [76]. The memory exceeds the threshold of pre- to postnatal life [77] and shapes postnatal preferences. It has been proven that third trimester fetuses are familiar with their mother’s language [78]: Newborns prefer to hear

the mother’s voice or the language or melodies spoken or sung by the mother which was demonstrated by sucking with a “sucky-dummy device” [79]. Sounds that resemble the intrauterine environment, but also music, encourage sucking and falling asleep of newborns [80, 81]. Pilot studies have also shown fetal behavioral changes when mothers listen to music with headphones only [82]. Whether fetuses are “enriched” more by direct exposure or maternal relaxation is difficult to distinguish when both are directly and simultaneously exposed to music after 22 weeks. In any case, music exposure during pregnancy promotes neuromotor skills in childhood [83] and stable behavior as compared to controls [83]. Prenatal musical experiences – mainly rhythmic elements – are still remembered after one year [84], although the time span of acoustic memory is shorter in newborns than in adults [85].

“Music is my first love, it will be my last”. This song by John Miles still applies in different cultures, as a number of proto-rhythms seem to be of biological prenatal origin [86]. The maternal voice represents a continuity from pre- to postnatal life [87, 88]. This relationship is “musical” since the child does not yet understand the meaning of language. Listening has an influence on voice formation, hence spectrographic images of the first cry of a newborn child are already similar to the patterns of the maternal voice [89]. Various devices are commercially available to expose fetuses to music programs, but we doubt that the music produced will reach the fetus, and the band to the mother is missing [90]. Lubetzki et al. [91] played Mozart music for premature babies between 32 and 37 weeks: As compared to a control group, energy consumption was reduced in those who listened to Mozart. In children with disabilities, music therapy was able to improve development, especially communicative skills [92]. Studies in adults support the hypothesis that musical abilities are inherent in every brain [93]. Even more important for a lifelong effect of music exposition are studies in which motor, sensory and cognitive abilities were examined in old age and classified according to whether the subjects had received music instruction in their youth for at least one year. Thus, it was confirmed that early stimulation of neuronal connections plays an essential role in maintaining cognitive abilities throughout lifetime. The longer the instruction took place, the less symmetrical and asymmetrical motor skills deteriorated [94].

About 1–2% of the human genome is assigned to the receptors of the olfaction and taste [95]. After the first trimester, the receptors of the olfactory organ in the upper nasal cavity are mature and connected to the brain by olfactory nerves [95, 96]. The dendrites grow into the mucosa of the mouth and nose binding chemical substances; the

signals are transmitted to the paleocortex and hippocampus [95]. Taste buds are scattered throughout the oral cavity from 12 SSW onwards, mainly on the tongue and the front palate [97]. During the second trimester, sensory cells spread on the nasal septum and transmit hormonal responses through pheromones. During the third trimester the olfactory organ is mature. From 10 gestational weeks onwards, amniotic fluid with odorous substances from mother and child pass through the nasal cavity by fetal respiratory movements [98]. Aromatic substances of the maternal diet can thus already influence the chemosensory function. Rat fetuses react more strongly to odorous substances in the amniotic fluid than in the air, since the amniotic fluid intensifies the chemosensory reaction [99]. In sheep, intranasal injection of odorous substances causes changes in FHR [96]. In humans, the intra-amnial injection of sweet or bitter substances causes changes in swallowing [97].

Long-term memory of odors and flavors has been shown in newborns of alcoholic mothers by increased reactivity to odor over 48 h compared to other newborns [100] without differences in the reaction to lemon [101]. Newborns prefer to suck on a breast previously coated with amniotic fluid from their mothers [95]; if the amniotic fluid differed, the babies oriented towards the odor of their own mother, which suggests an olfactory memory [100]. The smell of amniotic fluid calms children, who then scream less [102]. Newborns orient to the smell of their mothers reacting with breathing or facial movements [103]. This suggests that odors support social bonding, which is used in incubators for premature babies by giving them a stuffed animal that the mother carried. A habituation effect was described for repeated exposure to odors [103]. Smell and taste experiences might have therapeutic consequences to stabilize breastfeeding, adaptation, and bonding, and can also represent an extended form of “enrichment”.

Implications for future projects

Physical, mental, and social health is more than the absence of suffering but implies that people can unfold their genetic capabilities. Scientific projects help to link the fetal development with new insights of epigenetic processes and their significance for public health concepts. Exposure to adverse environments in early life, such as abnormal nutrition and maternal stress may reprogram organ development with potentially lifelong consequences and disrupt cellular functions contributing to accelerated aging and the potential risk of disease in older age [26].

Both animal and human data show that the uncontrollable impact of even ancestral adverse stress and trauma can potentially be offset by a beneficial experience throughout life [26].

Our motivation for designing creative projects was increased from a study showing that newborns of pregnant women with positive pregnancy experiences had increased telomere lengths, which may improve their chances of a longer life [104]. The bush fire in Alberta, Hurricane Harvey in Houston, and migrant family stress in Pforzheim were identified as study populations of vulnerable populations [12]. Creative writing of pregnant women has been used and shown that short episodes of expressive writing can improve cognitive outcome of the offspring [105, 106]. In a review by Olson et al. [12] it is described that children will be later examined for neuromotor outcome, metabolic biomarkers, and the risk for a later premature birth.

A Canadian team tracked the children of pregnant women who were exposed to increased stress before or during pregnancy during the 1998 ice storm in Quebec (“Project Ice Storm”). Between the ages of 2 and 10 years, the stress experience explained differences in speech characteristics, especially at early exposure, increasing rates of obesity, autism, pro-inflammatory markers, and altered DNA methylation up to 15 years. Exposure of pregnant women to flooding in Iowa (US) and in Queensland (Australia) found similar effects on cognitive and motor development or even obesity rates in the offspring [12].

Currently, the outbreak of the coronavirus disease exposes pregnant women to increased risks and fears.

A systematic review found 3,166 papers on this topic and then included 24 studies reporting negative psychological effects such as post-traumatic stress symptoms, confusion, and anger. Stressors included longer quarantine duration, infection fears, frustration, boredom, inadequate supplies, or financial loss. Some researchers have suggested long-lasting effects [107]. It has been shown that the exposure to COVID-19, combined with quarantine measures adversely affected the thoughts and emotions of mothers, worsening her depressive symptoms [11].

This all means that the need for screening for anxiety, stress, and depression in pregnant women who – as pointed out – may transmit the negative consequences to following generations has even increased in the whole population and not only the described vulnerable subgroups.

Already in 2002, the first author of this article proposed the design of trials addressing not only the wish to study the influence of music on developing children but also the desire to create concepts of a caring relationship by musical interventions and thus to fulfill the concept of

environmental, sensory and social enrichment. A variety of ideas how future interventions could be realized and evaluated was given, such as to evaluate parents' preferences, their wish to move or to sing and to perform these studies cross-culturally to evaluate further insights regarding anthropological perspectives. Simultaneously, it was proposed to focus on specific risk groups, to use questionnaires and biophysical methods to document instantaneous and long-term effects [108]. Thereafter, we have evaluated the musical behavior of mothers during pregnancy and proposed to compare intervention with control groups [109].

Unfortunately, as much as screening for genetic aberrations has been pushed forward and is combined with enormous costs but comparably only few options of therapy rather than pregnancy terminations, the screening for maternal characteristics that cause epigenetic diseases in the offspring which could be followed by preventive interventions are neglected.

Although the concept of the fetus as a patient demands that we have preventive ethical obligations not only for visible diseases but also for environments limiting potentials of healthy development and aging of the offspring, the most frequent reaction of obstetricians towards the importance of early interventions is rather characterized by "passive aggressive resistance" [110]. In contrast, it took only a noticeably short time to convince the Berlin Philharmonics and dedicated artists to help to create, design and realize acoustic enrichment programs for parents-to-be. Thus, we have the chance to offer concerts and workshops at two-week intervals from early pregnancy onwards within the Foyer of the Berlin Philharmonic chamber concert hall within a cohort and feasibility study and to evaluate psychological and biological consequences.

We needed time and perseverance to find and construct a research group of a satisfactory artistic and scientific level by integrating dedicated maternal-fetal medicine specialists, psychologists, epidemiologists, and artists. The initial common goal is to determine the compliance of parents-to-be, and to compare results of an intervention group with a pre-existing cohort. Further goals are whether creative interventions can counteract the harmful effects of maternal stressors and then to focus on specific interventions in vulnerable subgroups. Finally, we have the vision, to demonstrate the "survival value" of musical and social interventions, to decrease inequality and to extend the concept to a cross-cultural movement.

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described project not compromising in their humanistic, scientific, and artistic visions. Such projects are now desperately needed. We thank Prof. Olson from Edmonton, Canada, for helpful and sensitive interest from the OPERA (Optimal Environment Risk Assessment) group, Bettina Frei, head of the Berlin Philharmonic Educational Department and Raimar Orlovsky representing and organizing the musicians of the orchestra for being open to develop music programs and workshops to be performed for three years on Saturday mornings within the Foyer of the Berlin Philharmonic chamber music hall. Prof. Sonja Entringer from the Charité Berlin has already followed and evaluated biologic and psychologic markers in a Berlin cohort and Thorsten Braun is experienced in placental stress markers. They are both willing to cooperate by investing their clinical and laboratory skills. Clinicians from the Friedrichshain Vivantes hospital deliberately offered to help with non-invasive measurements of stress markers before and after the interventions. In advance, we thank Berlin midwives and colleagues who are happy to inform parents-to-be in the first trimester, e.g., in August and September 2021.

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