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RESEARCH SUMMARY

Association of Prenatal Exposure to Early-Life Adversity With Neonatal Brain Volumes at Birth. Regina L. Triplett, Rachel E. Lean, Amisha Parikh, J. Philip Miller, Dimitrios Alexopoulos, Sydney Kaplan, Dominique Meyer, Christopher Adamson, Tara A. Smyser, Cynthia E. Rogers, Deanna M. Barch, Barbara Warner, Joan L. Luby and Christopher D. Smyser. *JAMA Network Open* (2022), 5(4):e227045. DOI: 10.1001/jamanetworkopen.2022.7045

It is well known that children who experience severe stress, poverty or other forms of adversity when they are young are at increased risk of developing behavioural or psychological problems, and of poor health, later in life. However, the biological mechanisms through which early-life adversity (ELA) leads to these outcomes are not yet completely understood. Studies of human and animal brain development have suggested that there are differences in brain structure between children who have experienced ELA and their more fortunate peers. There appear to be clear links between poverty and stress in early childhood, brain structure and volume, and cognitive and behavioural difficulties.

However, despite the unique vulnerability of the brain in the prenatal period – the brain grows and develops exceptionally quickly during the second and third trimesters of pregnancy – little is known about whether, or how, expectant mothers’ experiences of adversity affect their infants’ brain development. Such studies as have been published have tended to focus on individual factors, such as smoking or substance abuse. Some studies have linked maternal stress during pregnancy to structural differences in their infants’ brains, but none have focused explicitly on socioeconomic factors.

Child poverty is higher in the USA than in most other developed countries, and mothers of young children there also have high rates of anxiety and depression. It is therefore likely that early-life adversity, including adversity experienced before birth, will affect a significant proportion of US children. An investigation of the effect of poverty and stress in pregnant women on the development of their infants’ brains is therefore overdue. A group of researchers led by Regina Triplett, a paediatric Neurologist at Washington University in St Louis, Missouri, USA have now begun to fill this gap with a large prospective study of mothers and their infants in that city.

Triplett and her co-workers recruited a total of 395 mothers attending obstetric clinics in St Louis between September 2017 and February 2020. After eliminating multiple births; premature, sick or low birthweight infants; and those born after the start of the COVID-19 pandemic a total of 280 pairs of mothers and healthy infants remained in the study. All mothers completed questionnaires during pregnancy and after delivery, and these, with their medical records, were used to assess their health and socio-economic status. Each infant's brain was scanned using magnetic resonance imaging (MRI) during the first weeks of life and while the baby was sleeping normally. These brain scans were used to estimate the volumes of the whole cortex, white matter, grey matter and cerebellum of each infant's brain, as well as those of the hippocampus and amygdala. These two brain regions are known to be involved in processing memories and emotions respectively. Finally, the MRI scans were used to estimate the extent to which each infant's cortex was folded, assessed using a numerical value called the gyrification index (GI). Cortical folding increases the surface area of the cortex, thereby increasing its potential functionality,

The researchers derived two simple numerical indicators for social disadvantage and maternal stress by combining sets of relevant measures. The social disadvantage measure included medical insurance status, income compared to needs and indices covering area deprivation and healthy eating. The stress measure combined readings from scales covering perceived stress, post-natal depression, anxiety and discrimination (the last named mainly referring to racial discrimination). A medical risk score was also calculated for each mother; tobacco use was assessed from the questionnaires and marijuana use partly from those and partly from urine screening. This was carried out on a representative sub-sample of the mothers only, during routine obstetric care.

A complex statistical analysis showed that the four variables that were most closely correlated with differences in brain volumes were the infant's sex; maternal tobacco use; birth weight; and the infant's postmenstrual age (PMA) at the time of the MRI scan. This is a measure of infant age that corrects for prematurity, defined as the time between the mother's last menstrual period and the infant's scan. Once these variables had been corrected for, however, there was still a clear correlation between social disadvantage and brain volume, with more disadvantaged infants having smaller overall brain volumes as measured in the MRI scan, smaller volumes of each of the subregions measured and smaller GI values. There was no further significant reduction in the volume of the hippocampus or the amygdala with disadvantage once overall brain size had been corrected for; instead, the feature with the strongest correlation with social disadvantage was the volume of white matter. This term refers to areas of the cortex where the nerve axons are coated with fatty myelin, which gives it a light appearance. It is associated with learning and some other higher brain functions, and its early development is known to be affected by stress. Interestingly, there was no significant correlation between the chosen measure of maternal stress and any of the brain variables.

The exact mechanism or mechanisms through which the poverty and other social disadvantage experienced by pregnant women affects their infants' brain development is not fully known. Triplett and her colleagues speculate that this might arise from the over-stimulation of the hypothalamic–pituitary–adrenal (HPA) axis, leading to increased production of the stress hormone, cortisol. Adversity may also lead to changes in a mother's immune system, any of which might affect foetal brain development. Although these mechanisms can be assumed to be triggered by any form of stress, women living in poverty may also suffer from deficits in micronutrients or from exposure to pollution, either of which may exacerbate such processes.

The researchers conclude that the associations between poverty and brain development that have been identified in older infants and children are clearly evident in the first weeks of life, suggesting that they began before birth. They identify some specific variables that it will be worth exploring further, including race – which correlates very closely with social disadvantage – and exposure to pollution, and suggest that these findings may help design interventions to improve infant brain development by focusing on the key role of material disadvantage in the prenatal and very early postnatal period.

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