Sex differences in brain in response to midlife stress linked to fetal stress exposures

5 April 2021

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Men and women whose mothers experienced stressful events during pregnancy regulate stress differently in the brain 45 years later, results of a long-term study demonstrate.

In a unique sample of 40 men and 40 women followed from the womb into their mid-forties, the brain imaging study showed that exposure during fetal development to inflammation-promoting natural substances called cytokines, produced by mothers under negative stress, results in sex-associated differences in how the adult brain responds to negative stressful situations more than 45 years after birth, reports Jill M. Goldstein, Ph.D., founder and executive director of the Innovation Center on Sex Differences in Medicine (ICON) at Massachusetts General Hospital (MGH) and her co-authors.

The researchers found that abnormal levels of pro-inflammatory cytokines produced in mothers during pregnancy and the balance between pro-inflammatory and anti-inflammatory cytokines affect brain development differences by sex in their offspring that continue throughout life.

The findings are published in *Proceedings of the National Academy of Sciences* (*PNAS*).

"We know that there are developmental roots to major psychiatric disorders such as depression, schizophrenia and bipolar disorder, and we know that these roots begin in fetal development. We also know these disorders are associated with abnormalities in the brain circuitry that regulates stress—circuitry that is intimately tied to regulating our immune system," says Goldstein, a professor of Psychiatry and Medicine at Harvard Medical School. "Given that the stress circuitry consists of regions that develop differently in the male and female brain during particular periods of gestation and they function differently across our lifespans, we hypothesized that dysregulation of this circuitry in prenatal development would have lasting differential impact on the male and female brain in people with these disorders. We were particularly interested in the role of the immune system, in which some abnormalities are shared across these disorders."

Goldstein and colleagues used functional magnetic resonance imaging, which measures brain activity by showing differences in blood flow within and between different areas of the brain. The researchers found that exposure to pro-inflammatory cytokines in the womb was associated with sex differences in how areas of the brain are activated and communicate with one another under negative stressful conditions in midlife.

For example, they found that in both sexes, lower maternal levels of tumor necrosis factor-alpha

(TNF?) a pro-inflammatory cytokine, were significantly associated with higher activity in the hypothalamus, a region of the brain that, among other functions, coordinates brain activity that regulates the release of stress hormones, like cortisol.

In contrast, lower levels of TNF? were also associated with more active communication between the hypothalamus and the anterior cingulate in men only. The anterior cingulate is an area of the brain associated with impulse control and emotion.

In women only, higher prenatal exposure to interleukin-6, another inflammatory cytokine, was associated with higher levels of activity in the hippocampus, a brain region important for inhibitory control of arousal.

Lastly, they found that the ratio between TNF? and the anti-inflammatory cytokine interleukin-10 was associated with sex-dependent effects on activity in the hypothalamus and its communication with the hippocampus, which provides inhibitory control of arousal in the hypothalamus under stress.

"Given that these psychiatric disorders are developing differently in the male and female brain, we should be thinking about sex-dependent targets for early therapeutic intervention and prevention," says Goldstein.

More information: Jill M. Goldstein el al., "Impact of prenatal maternal cytokine exposure on sex differences in brain circuitry regulating stress in offspring 45 years later," *PNAS* (2021). www.pnas.org/cgi/doi/10.1073/pnas.2014464118

Provided by Massachusetts General Hospital