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Neuroimaging reveals lasting brain deficits in iron-deficient piglets

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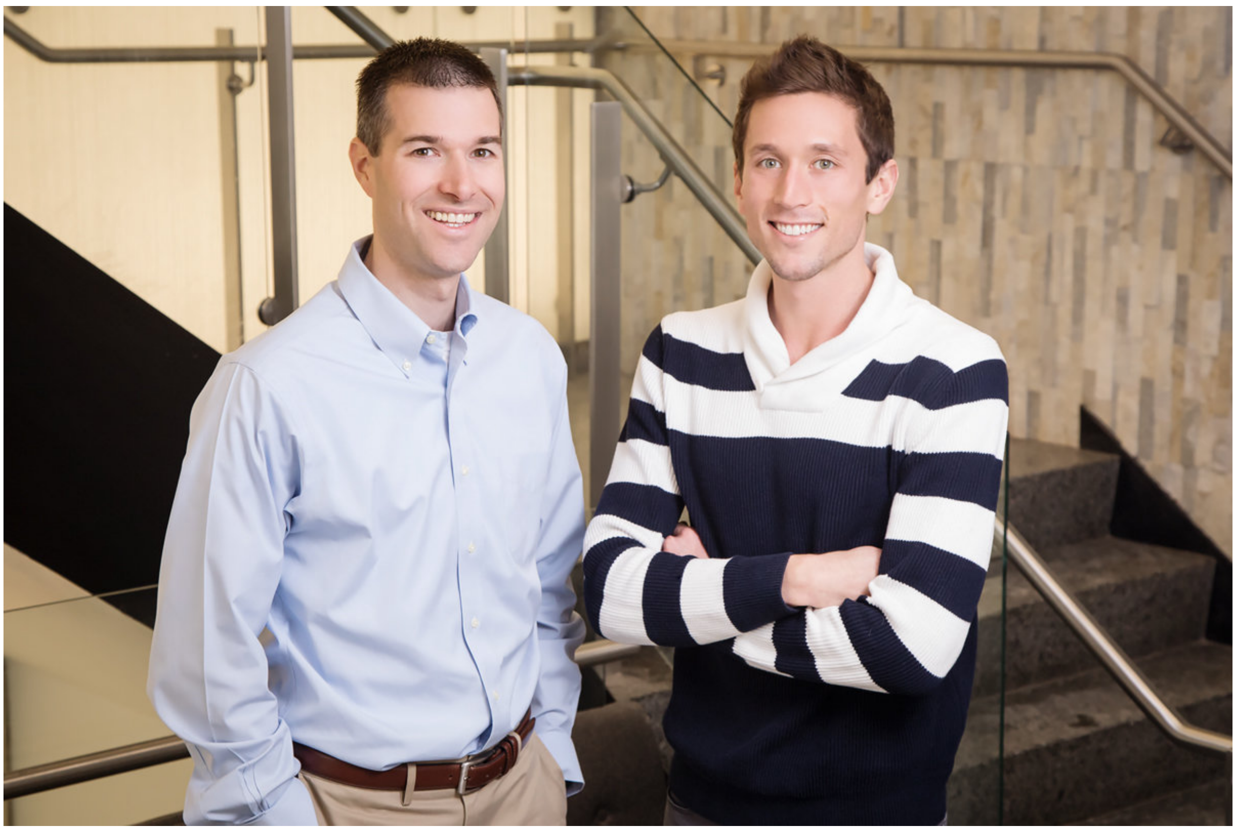

Animal sciences professor Ryan Dilger, left, graduate student Austin Mudd and their colleagues used neuroimaging to study how iron deficiency influences piglet brain development. The findings may have implications for human infant brain development. Credit: L. Brian Stauffer

Iron deficiency in the first four weeks of a piglet's life - equivalent to roughly four months in a human infant - impairs the development of key brain structures, scientists report. The abnormalities remain even after weeks of iron supplementation begun later in life, the researchers found.

The discovery, reported in the journal *Nutrients*, adds to the evidence that iron deficiency early in life can have long-lasting consequences for the brain, said University of Illinois animal sciences professor Ryan Dilger, who led the study with Austin Mudd, a graduate student in the neuroscience program at the U. of I. The analysis, which relied on neuroimaging to study the piglets' brains as they matured, homed in on specific brain regions most affected by iron-deficient diets. The use of neuroimaging was part of an effort to find noninvasive ways of studying pig brain development that could also be applied in humans.

Pigs are useful models for studies relevant to human health because they have some of the same nutrient and metabolic requirements as humans, Mudd said. For this reason, health authorities require that new infant formulas be tested in piglets before they can be used in clinical trials of human babies.

Pigs also have anatomically similar brains to humans, the researchers said.

"Pig brains and human brains follow very similar developmental trajectories," Mudd said. "One week of piglet brain growth is roughly equivalent to one month of human brain growth. You can overlay those trajectories and they are almost identical."

Pigs and humans also appear to respond in similar ways to dietary deficiencies - in particular, iron deficiencies, Dilger said.

"Nothing is as overt as an iron deficiency," he said. "Both piglets and human infants with iron deficiencies are smaller, and they display other characteristic anomalies. Iron deficiency in humans is the most prolific deficiency the world over."

"Research in humans has shown that iron deficiency early in life results in delayed motor development by 10 months of age, delayed cognitive processing by 10 years of age, altered recognition memory and executive functions at 19 years of age, and poorer emotional health in the mid-twenties" the researchers wrote.

In an earlier study of the same 28 piglets used in the new analysis, the scientists found that those fed iron-deficient diets for the first four weeks of life had smaller overall brain volume than those fed an iron-sufficient diet. When the iron-deficient pigs switched to an iron-replete diet from four to eight weeks of life, their brain volumes caught up with those of pigs that had never been iron deficient. This might lead some to assume that iron supplementation later in life corrects all of the problems associated with earlier deficiencies, Mudd said.

"We know, however, that there are many different brain regions and each one of them develops at a different rate. There could be a critical window of development for one region and not another," he said. "With our neuroimaging, we can look more closely at different brain structures and start to identify those developmental windows."

The researchers used magnetic resonance imaging and other noninvasive techniques to determine the relative iron content, volume and structural integrity of specific brain regions.

By comparing piglets with and without iron-deficient diets in the first four weeks of life, and then again at eight weeks after all received sufficient iron for four weeks, the researchers were able to determine whether the brain anomalies seen at four weeks persisted after the iron-deficient piglets' diets were corrected.

The analysis revealed that the brains of iron-deficient piglets did not fully recover. They had reduced iron content in several brain regions, including the left hippocampus, a region essential to learning and memory. Giving the piglets an iron-replete diet for another four weeks did not appear to increase the iron content of these brain regions.

The iron-deficient piglets also had structural deficiencies in their gray matter and white matter in several brain regions at four and eight weeks. Only the olfactory bulb, a brain structure that supports the sense of smell, was bigger in the iron-deficient piglets than in those that had never been deficient. The olfactory bulbs of the deficient piglets also had greater iron content than those of piglets that had never been deficient.

This latter finding suggests there could be a compensatory mechanism in the brain that concentrates available iron in the olfactory bulb to encourage an animal that normally roots around in the dirt with its snout to do so more aggressively to obtain sufficient iron from soil, the researchers said. While this is only a hypothesis and has not been proved, the researchers said, it is interesting that humans with iron deficiencies sometimes experience a condition known as pica, which makes them want to eat unusual substances, including dirt.

"Essentially what we found in this study is that there is a critical window in development for providing iron, and that window is immediately after birth," Mudd said. More research must be done to determine if this is also true for human infants, he said.

More information: Austin Mudd et al, Early-Life Iron Deficiency Reduces Brain Iron Content and Alters Brain Tissue Composition Despite Iron Repletion: A Neuroimaging Assessment, *Nutrients* (2018). DOI: 10.3390/nu10020135

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