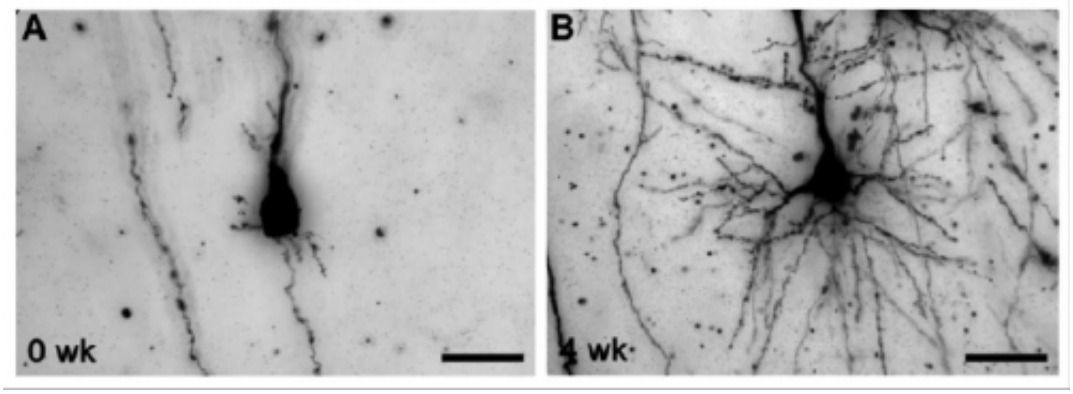
# Study findings have potential to prevent, reverse disabilities in children born prematurely

January 17 2013



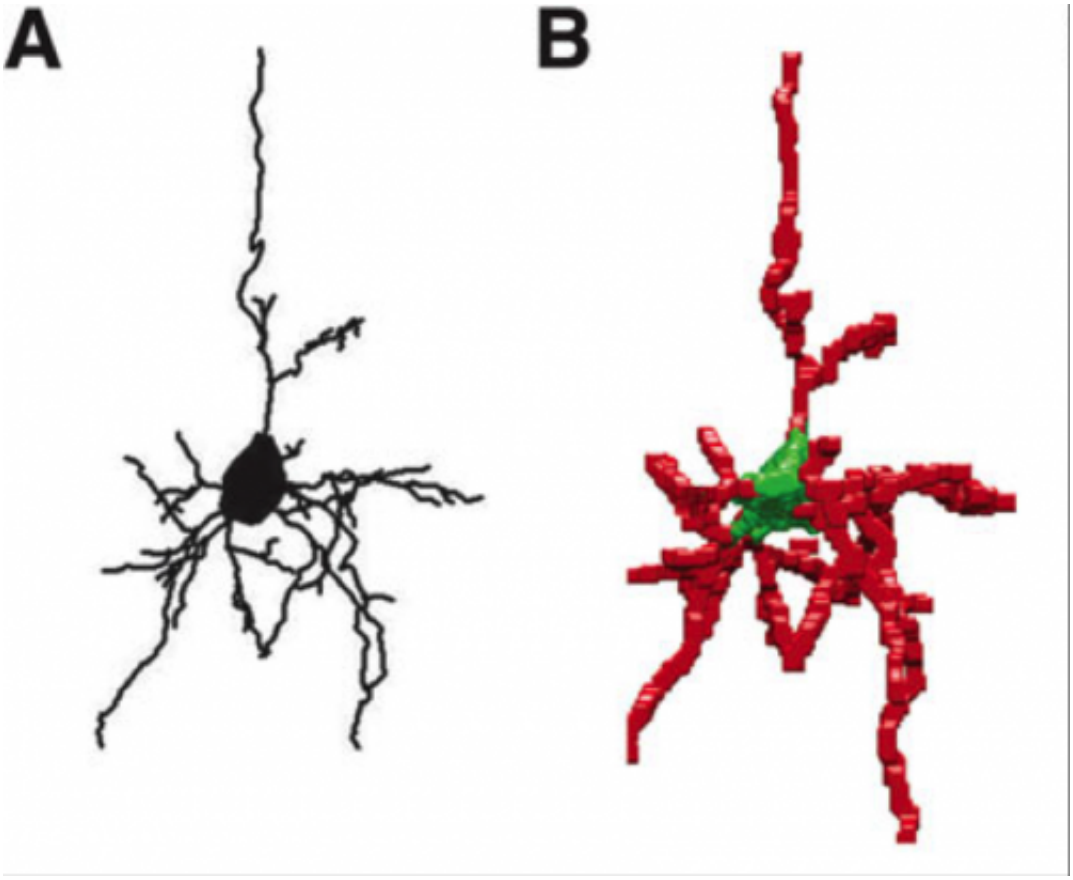

During normal brain development in our fetal model, neurons (brain cells) rapidly grow processes called dendrites that allow them to communicate with other neurons. In panel A, a neuron equivalent to that from a 28-week-old human fetus displays very few dendritic processes and appears very simple. Panel B shows that four weeks later, neurons appear to be much more complex with many dendritic processes and branches present. Credit: Oregon Health & Science University

Physician-scientists at Oregon Health & Science University Doernbecher Children's Hospital are challenging the way pediatric neurologists think about brain injury in the pre-term infant. In a study published online in the Jan. 16 issue of *Science Translational Medicine*, the OHSU Doernbecher researchers report for the first time that low blood and

oxygen flow to the developing brain does not, as previously thought, cause an irreversible loss of brain cells, but rather disrupts the cells' ability to fully mature. This discovery opens up new avenues for potential therapies to promote regeneration and repair of the premature brain.

"As neurologists, we thought ischemia killed the neurons and that they were irreversibly lost from the brain. But this new data challenges that notion by showing that ischemia, or low blood flow to the brain, can alter the maturation of the neurons without causing the death of these cells. As a result, we can focus greater attention on developing the right interventions, at the right time early in development, to promote neurons to more fully mature and reduce the often serious impact of preterm birth. We now we have a much more hopeful scenario," said Stephen Back, M.D., Ph.D., lead investigator and professor of pediatrics and neurology in the Papé Family Pediatric Research Institute at OHSU Doernbecher Children's Hospital.

Researchers at OHSU Doernbecher have conducted a number of studies in preterm fetal sheep to define how disturbances in brain blood flow lead to injury in the developing brain. Their findings have led to important advances in the care of critically ill newborn infants.



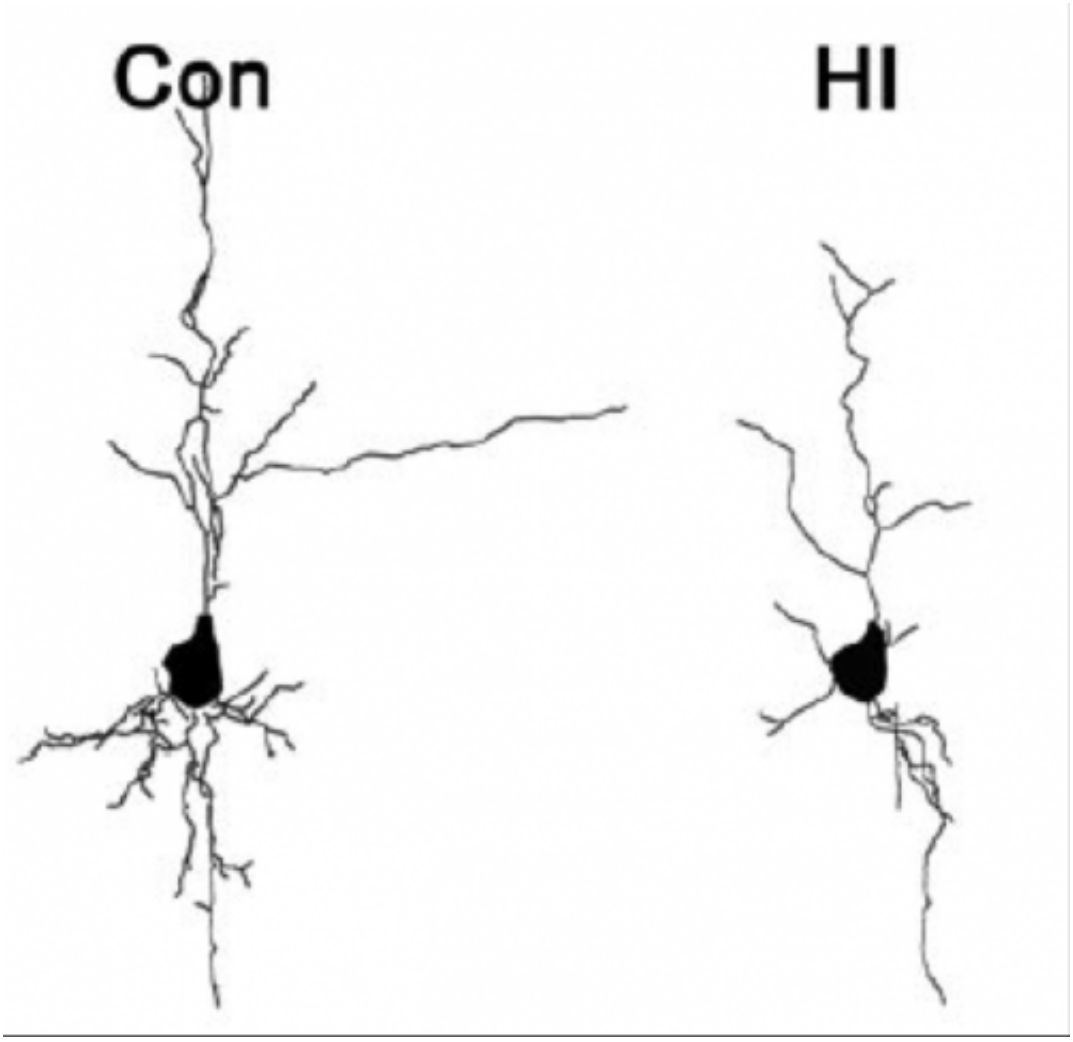

In the companion paper by Vinall et al., MRI anisotropy measurements of water diffusion demonstrated that human cortical development is abnormal in survivors of preterm birth. Here we address the cellular basis for the abnormal cortical MRI. The figure on the left (A) is the cortical neuron tracing that was used to generate the 3D structure on the right (B). From the 3D structure in B, a calculation of theoretical water diffusion along the cell?s processes was generated. With this approach, it was determined that water diffusion (anisotropy) was abnormal in the immature cells from the ischemic animals when compared with controls. The anisotropy disturbances predicted from the cell-based calculations were in close agreement with the anisotropy disturbances detected by MRI of the cerebral cortex. Credit: Oregon Health & Science University

For this study, Back and colleagues used pioneering new MRI studies that allow injury to the developing brain to be identified much earlier

than previously feasible. They looked at the cerebral cortex, or "thinking" part of the brain, which controls the complex tasks involved with learning, attention and social behaviors that are frequently impaired in children who survive preterm birth. Specifically, they observed how brain injury in the cerebral cortex of fetal sheep evolved over one month and found no evidence that cells were dying or being lost. They did notice, however, that more brain cells were packed into a smaller volume of brain tissue, which led to, upon further examination, the discovery that the brain cells weren't fully mature.

In a related study published in the same online issue of *Science Translational Medicine*, investigators at The Hospital for Sick Children and the University of Toronto studied 95 premature infants using MRI and found that impaired growth of the infants was the strongest predictor of the MRI abnormalities, suggesting that interventions to improve infant nutrition and growth may lead to improved cortical development.

"I believe these studies provide hope for the future for preterm babies with brain injury, because our findings suggest that neurons are not being permanently lost from the human cerebral cortex due to ischemia. This raises the possibility that neurodevelopmental enrichment—or perhaps improved early infant nutrition—as suggested by the companion paper, might make a difference in terms of improved cognitive outcome," Back said.




When fetal brains are exposed to decreased oxygen and blood flow (hypoxia and ischemia), the neurons do not appear to mature normally. On the left is a tracing of a brain cell (neuron) from a control (Con) animal showing normal development of its complex branching pattern. On the right is a tracing of a neuron of the same age as the control, which was exposed to a brief period of hypoxia/ischemia (HI). This cell displays fewer processes and a simpler branch pattern. Thus, despite being the same age as the control animal, brain cells in the HI animal are more immature. Credit: Oregon Health & Science University

"Together, these studies challenge the conventional wisdom that preterm birth is associated with a loss of cortical neurons. This finding may

change the way neurologists think about diagnosing and treating children born prematurely," said Jill Morris, Ph.D., a program director at the National Institute's of Health's National Institute Neurological Disorders and Stroke.

More than 65,000 premature babies are born in the United States each year. Children who survive preterm birth commonly suffer from a wide range of life-long disabilities, including impaired walking due to cerebral palsy. Currently, children have a 10 times greater risk of acquiring cerebral palsy than of being diagnosed with cancer. By the time they reach school age, between 25 and 50 percent of children born prematurely are also identified with a wide range of learning disabilities, social impairment and attention deficit disorders.

Provided by Oregon Health & Science University