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Sugar-burning in the adult human brain is associated with continued growth, and remodeling

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Although brain growth slows as individuals age, some regions of the brain continue to develop for longer than others, creating new connections and remodeling existing circuitry. How this happens is a key question in neuroscience, with implications for brain health and neurodegenerative diseases. New research published today shows that those areas of the adult brain that consume more fuel than scientists might expect also share key characteristics with the developing brain. Two Allen Brain Atlas resources – the Allen Human Brain Atlas and the BrainSpan Atlas of the Developing Human Brain – were crucial to uncovering the significance of these sugar-hungry regions.

The results are published this month in the journal *Cell Metabolism*.

"These experiments and analysis represent the first union of its kind between functional imaging data and a biological mechanism, with the Allen Brain Atlas resources helping to bridge that gap," comments Michael Hawrylycz, Ph.D., Investigator with the Allen Institute for Brain Science and co-author of the study. Data from PET scans provides structural insight into the brain, but until now, has not been able to elucidate function. "Now we can make the comparison between the functional data and the gene expression data," says Hawrylycz, "so instead of just the 'where,' we now also have the 'what' and 'how.'"

The brain needs to constantly metabolize fuel in order to keep running,

most often in the form of glycolysis: the breaking down of stored sugar into useable energy. PET scans of the brain, which illuminate regions consuming sugar, show that some select areas of the brain seemed to exhibit fuel consumption above and beyond what was needed for basic functioning. In cancer biology, this same well-known phenomenon of consuming extra fuel—called "aerobic glycolysis"—is thought to provide support pathways for cell proliferation. In the brain, aerobic glycolysis is dramatically increased during childhood and accounts for as much as one third of total brain glucose consumption at its peak around 5 years of age, which is also the peak of synapse development.

Since aerobic glycolysis varies by region of the brain, Hawrylycz and co-author Marcus Raichle, Ph.D., at Washington University in St. Louis, wondered whether regions of the brain with higher levels of aerobic glycolysis might be associated with equivalent growth processes, like synapse formation. If so, this would point to aerobic glycolysis as a reflection of "neoteny," or persistent brain development like the kind that takes place during early childhood.

In order to delve into the significance of aerobic glycolysis, researchers examined the genes expressed at high levels in those regions where aerobic glycolysis was taking place. The team identified 16 regions of the brain with elevated levels of aerobic glycolysis and ranked their neotenous characteristics. True to prediction, they found that gene expression data from those 16 regions suggested highly neotenous behavior.

The next phase was to identify which genes were specifically correlated with aerobic glycolysis in those regions. The Allen Brain Atlas resources proved crucial in this task, helping to pinpoint gene expression in different regions at various points in development. The Allen Human Brain Atlas was used to investigate the adult human brain, while the BrainSpan Atlas of the Developing Human Brain, developed by a

consortium of partners and funded by the National Institutes of Health, provided a window into how gene expression changes as the brain ages.

Analysis of the roles of those genes pointed clearly towards their roles in growth and development; top genes included those responsible for axon guidance, potassium ion channel development, synaptic transmission and plasticity, and many more. The consistent theme was development, pointing to aerobic glycolysis as a hallmark for neotenous, continually developing regions of the brain.

"Using both the adult and developmental data, we were able to study gene expression at each point in time," describes Hawrylycz. "From there, we were able to see the roles of those genes that were highly expressed in regions with aerobic glycolysis. As it turns out, those genes are consistently involved in the remodeling and maturation process, synaptic growth and neurogenesis—all factors in neoteny." "The regions we identified as being neotenous are areas of the cortex particularly associated with development of intelligence and learning," explains Hawrylycz. "Our results suggest that aerobic glycolysis, or extra fuel consumption, is a marker for regions of the brain that continue to grow and develop in similar ways to the early human brain."

More information: Goyal MS, Hawrylycz M, Miller JA, Snyder AZ, Raichle ME. Aerobic glycolysis in the human brain is associated with development and neotenous gene expression. *Cell Metabolism*, Jan. 7, 2014.

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