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Pathways toward and away from a metabolic cliff during brain aging

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An Editorial on the Frontiers in Science Lead Article
Breakdown and repair of metabolism in the aging brain

Key points

- Elucidating the complex relationships between brain metabolism, neural activity, and blood flow is vital to better understanding age-related neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease.
- By mining large datasets of human brain metabolic pathways and gene expression in young and older brains, and modeling how age-related changes affect neuronal excitability, a comprehensive new model by Shichkova et al. revealed critical molecular nodes that may determine whether brain health is maintained during aging.
- Major findings include insights into the metabolic resilience of young brains, age-related dysregulation of neuronal firing, and the role of estrogen-related receptor α (ESRRA) in brain aging and neuronal network activity.
- This freely available model offers a means to test hypotheses on how specific genes, environmental factors, diseases, pharmacological agents, and lifestyle factors affect neural metabolic networks and brain function and thus the development of neurodegenerative disorders.

Aging manifests as an inexorable decline in the function of all organ systems owing to dysregulation of, and damage to, their cellular components. Scientists have identified numerous alterations that occur in cells throughout the body and brain during aging. These include the following: genomic instability; oxidative damage to DNA, proteins, and cell membranes; the accumulation of aggregated proteins and dysfunctional mitochondria; the impaired ability of cells to repair molecular damage; impaired autophagy; and decrements in signaling pathways that normally bolster a cell's ability to cope with stress (1). These aging processes render humans vulnerable to a range of diseases, including cancers, diabetes, cardiovascular disease, neurodegenerative disorders, and infections.

Similar to the decline in physical capabilities, the performance of the human brain begins to decline during the third and fourth decades of life. Many people develop a catastrophic neurodegenerative disorder such as Alzheimer's disease (AD) or Parkinson's disease (PD) when they are in their 70s and 80s. In fact, by the age of 85, around half of all people will have one of these brain disorders. Neurons in the brain are particularly vulnerable to dysfunction and degeneration during aging, in part because their electrical activity generates high levels of oxidative and metabolic stress. The brain consists of complex networks of hundreds of billions of neurons, glial cells, and blood vessels that must communicate with each other in a highly integrated manner to support the energy requirements and functions of this organ. There is a tight coupling of neuron activity and blood flow, with glial cells serving an intermediary role in this process (2). These complexities pose a major challenge for the brain during aging, but it is unclear how energy metabolism becomes disrupted during aging and if and how this disruption contributes to functional decline or susceptibility to AD and PD.

In their lead article, Polina Shichkova, Henry Markram, and colleagues tapped publicly available databases and used sophisticated modeling methods to tackle the complicated problem of energy metabolism and brain aging (3). They performed a large-scale analysis of nearly 17,000 interactive biochemical pathways involved in regulating neuronal excitability, energy metabolism, and neuron–glia–blood vessel coupling during brain aging in humans. Their analyses included all nutrient and ion transporters, enzymatic pathways, and intercellular signaling pathways critical for neural network activity. Importantly, they also modeled these metabolic factors in both active (firing) and resting neurons. There were numerous novel findings, many of which can only be appreciated by a thorough interrogation of the data and the authors' discussion of their results. Here, I highlight several of their major findings and their implications.

A comparison of the interaction networks from young and old brains revealed a novel and very interesting general effect of aging. In the young brain the impact of one pathway on all other pathways is evenly distributed, whereas in the old brain interaction pathways exhibit clustering. The authors interpret this to mean that brain metabolism is more robust in the young brain because it has ways of adapting to physiological challenges such as stress or physical exercise (i.e., greater flexibility). A decline in metabolic flexibility during aging is consistent with evidence for age-related brain insulin resistance and impaired neuronal glucose utilization (4). In addition to revealing the consequences of aging on brain metabolic pathways and their impact on the control of neuronal network activity, the findings of Shichkova et al. may explain why stress resilience and recovery from traumatic brain injury or stroke are generally better in young people than in old people (5).

When neurons are active, they produce more adenosine triphosphate (ATP), which is critical for them to restore and maintain the electrical charge potential across their outer membrane. Neurons must "pump" positively charged sodium ions (Na^+) from their inside to their outside to maintain their resting membrane potential, requiring large amounts of ATP. By mapping age-related changes in pathways onto neuronal activity, Shichkova et al. identified reduced expression of the Na^+ pump protein as a pivotal cause of age-related dysregulation of neuronal firing (3). An age-related decline in Na^+ pump activity may also help explain why some people develop AD but others do not. Indeed, converging lines of evidence suggest aberrant neuronal network excitability and excitotoxic neuron damage play important roles in AD, with the neurons that have the highest firing rates—i.e., gamma-aminobutyric acid (GABA)ergic inhibitory neurons—being the most vulnerable to aging and AD (6).

Intriguingly, Shichkova et al. identified a transcription factor called estrogen-related receptor α (ESRRA) as a major focal point in age-related alterations in brain metabolic networks. ESRRA is known to regulate genes encoding proteins involved in fatty acid metabolism, mitochondrial function, and autophagy. Interrogation of the STRING functional protein association network database revealed multiple proteins associated with ESRRA, including those involved in adaptive cellular stress responses, mitochondrial function and quality control, and epigenetic regulation of neuroplasticity. This is the first piece of evidence of ESRRA playing a major role in brain aging and neuronal network activity. However, a prior comparison of brain regional gene expression in mice identified ESRRA as a potential regulator of adaptive responses of the brain to social stress (7). It will be of considerable interest to determine whether experimental upregulation of ESRRA can protect the brain against stress and aging.

While the rate of brain aging varies among individuals, the trajectory for all people tends toward a neuronal metabolic cliff and dementia. Efforts to avoid or even climb back up the metabolic cliff with interventions that bolster brain bioenergetic systems are in progress (8). Using an unguided optimization search, Shichkova et al. (3) revealed several therapeutic strategies already being pursued, including treatments that increase levels of the ketone β-hydroxybutyrate or nicotinamide adenine dinucleotide (NAD^+), both of which play different pivotal roles in metabolism. Their model also supports evidence that physical exercise, intermittent fasting, and regular participation in intellectual challenges can each promote a more youthful profile of the brain's metabolic networks (9–11). This new and freely available model provides an opportunity for investigators in various disciplines to test hypotheses concerning whether and how specific genes, environmental factors, diseases, pharmacological agents, and lifestyle factors impact neural metabolic networks and brain function.

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