Researchers develop age prediction model for human brain tissue using artificial intelligence

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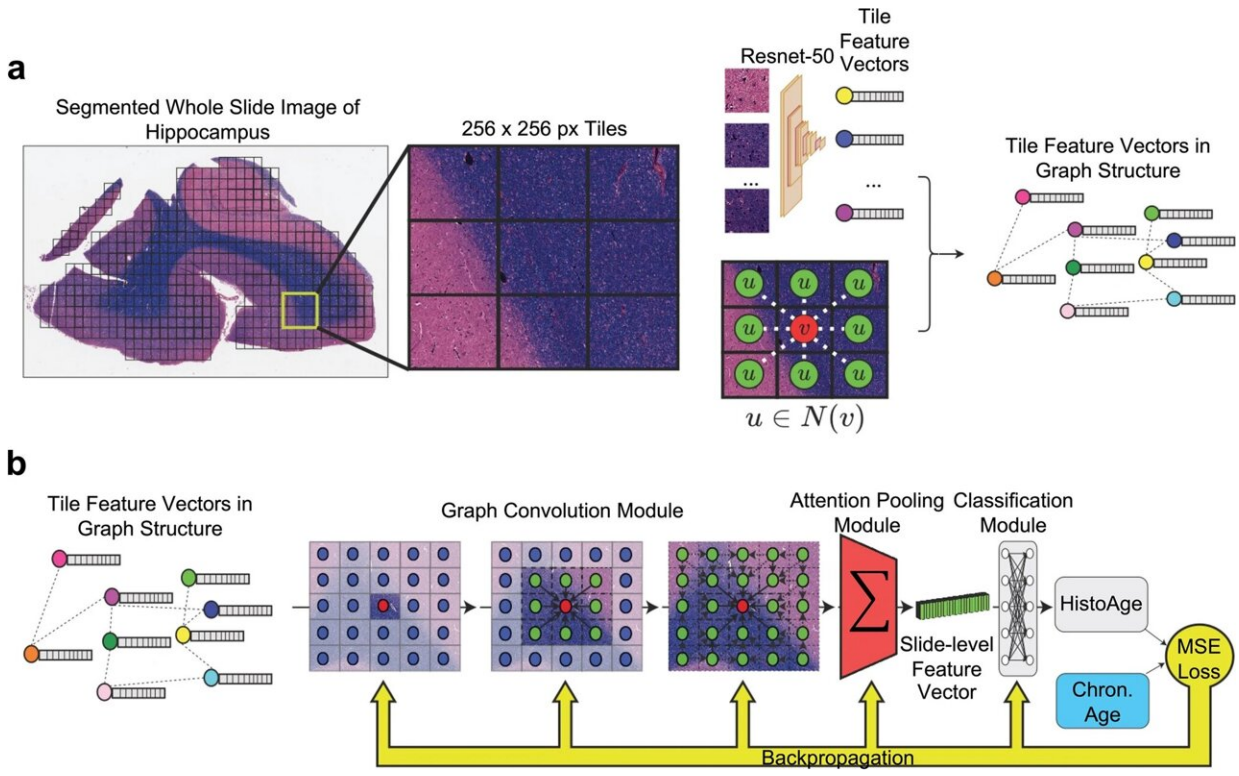

Schematic of preprocessing and model training. **a** Preprocessing: whole slide images (WSI) are segmented into 256 × 256 pixel tiles, removing areas without tissue. The tiles are then passed through an Imagenet pretrained Resnet-50 convolutional neural network, which yields feature vectors. Finally, the WSI is represented as a graph where each node is a tile encoded into a feature vector, with edges between tiles that are adjacent in slide space. **b** Model training: the WSI represented as a graph structure is passed through a graph convolution model, which learns not only the features of each tile but also messages passing

between tiles, integrating macroscale information along with microscopic information. This is then passed through an attention pooling module, which pools all the tile feature vectors into a single slide-level feature vector. This is then passed through a classification model, which estimates HistoAge. HistoAge is taken with chronologic age and the mean-squared error (MSE) loss is used to update the weights of the model. Credit: *Acta Neuropathologica* (2023). DOI: 10.1007/s00401-023-02636-3

The aging brain undergoes structural and cellular changes that can impact function and increase susceptibility to neurodegenerative disorders like Alzheimer's disease. Age acceleration—or the differences between biological and chronological age—in the brain can reveal insights about mechanisms and normal functions of one of the body's most important organs. It can also explain age-related changes and functional decline, as well as identify early changes related to diseases, indicating the onset of a brain disorder.

Mount Sinai researchers say they have, for the first time ever, used AI to develop an algorithm they term "HistoAge" which predicts age at death based on the cellular composition of human brain tissue specimens with an average accuracy of within 5.45 years. This powerful tool can also identify neuroanatomical regions vulnerable to age-related changes, an indicator of potential cognitive diseases.

The researchers examined a collection of almost 700 digitized images of slides with human hippocampal sections from aged brain donors to develop the histological brain age estimation algorithm. The hippocampus is known to be involved in both brain aging and age-dependent neurodegenerative diseases, and thus is an ideal region for this analysis.

The team then trained a machine learning model to estimate a person's

age at death based solely on the digitized section, a task that is impossible for a human observer to perform with any degree of accuracy. They used the difference between the model-predicted age and actual age to derive the amount of age acceleration in the brain.

When compared with current measures of age acceleration (e.g., DNA methylation), they found that HistoAge-based age acceleration had stronger associations with cognitive impairment, cerebrovascular disease, and the levels of Alzheimer's-type abnormal degenerative protein aggregation. The study found that the HistoAge model is a reliable, independent metric for determining brain age and understanding factors that drive neurodegeneration over time.

The researchers said the HistoAge model, and other subsequent similar algorithms, represent an entirely new paradigm for assessing aging and neurodegeneration in human samples and can easily be deployed at scale in clinical and translational research laboratories. Further, this approach provides more rigorous, unbiased and robust metrics of cellular changes underlying degenerative diseases.

The team will next build a multicenter collaboration to develop a large AI-ready dataset that will be used to develop even more powerful AI models that have the potential to transform and enhance our understanding of brain diseases.

Mount Sinai's Dr. Crary said of the research, "AI's disruptive influence on brain research is a paradigm shift propelling us towards the next generation of cures. The HistoAge model will enable us to uncover crucial causal aspects of debilitating brain diseases such as Alzheimer's disease."

Said Mount Sinai's Dr. Farrell, "Using the latest computational approaches, like AI, on human tissue samples from Mount Sinai's vast

and diverse collections is a shift in the way we assess human diseases. Our novel HistoAge model is just one example of the way AI is paving the way for further discovery about the mechanisms of aging and neurodegeneration."

"Clinical scientists are increasingly using AI in research and diagnostic settings. It's a tool that is revolutionizing medicine and we are excited to be leaders in this space, optimizing machine learning—not to replace our Health System's commitment to compassionate care, but to improve diagnosis and treatment for all patients."

According to Mount Sinai's Dr. Marx, "This model opens the floodgates for a slew of fascinating and essential analyses that bring us closer to finally understanding the aging brain and age-related brain diseases such as Alzheimer's. This is the first time we have been able to put a number to how much aging there is in the brain in pathology. With this approach, we can discover genes that protect against brain aging or genes that make aging worse in the brain, as well as discover the environmental risk factors that make individuals' brains age faster."

The study is published in the journal *Acta Neuropathologica*.

More information: Gabriel A. Marx et al, Histopathologic brain age estimation via multiple instance learning, *Acta Neuropathologica* (2023). DOI: 10.1007/s00401-023-02636-3

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