Predicting brain age across the lifespan: Models, applications and challenges

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Overview

Using machine learning techniques, predictive models of brain age derived from brain images can infer apparent biological age of a person's brain based on brain structure and/or function. A person's brain age can vary markedly from their chronological age and the age at which individual trajectories diverge from the population norms can reflect key characteristics of brain health from early childhood to old age. Indeed, a body of literature has shown delayed brain age in autism spectrum disorder and attention-deficit hyperactivity disorder, whereas advanced brain age often relates to schizophrenia, bipolar disorder, major depression disorder, dementia and multiple sclerosis as well as poorer cognitive ability.

However, many technical and conceptual challenges remain in accurately predicting brain age and appropriately interpreting brain age gaps. Key challenges include the choice of machine learning algorithms (e.g., regression vs deep learning; linear vs non-linear); the choice of neuroimaging features (e.g., structure vs function; ROIs vs vertices); and the correction for age-biases in brain age prediction. Conceptual challenges include whether brain age captures underlying brain physiology or simply noise (i.e., prediction error); and whether individual differences in brain age emerge early in life or capture ongoing brain changes.

The symposium brings together four internationally recognized experts in neuroimaging and brain aging to discuss recent advances in addressing these important issues associated with brain age prediction. As such, our symposium is timely and will appeal to a broad cross-section of attendees. Our symposium will appeal to both methodologists focussed on developing and optimizing machine learning models for improved accuracy of brain age prediction, and neuroscientists and clinicians interested in applying these models to understand brain development and aging in health and disease.

Lecture 1: *Brain age models of development and aging in mood and anxiety disorders*

Laura Han Presenter

Normal brain development involves coordinated and sequenced maturation events that are defined by growth and eliminative processes. At the same time, mental disorders are increasingly conceptualized as disorders that may arise due to deviations from this normal brain development, representing a promising research avenue. Previous studies have shown that adults with mood and anxiety disorders have brain patterns that correspond to brains that are usually observed at older ages. However, brain changes in adolescence (i.e., development) are markedly different from age-related brain changes in adulthood (i.e., aging). This begs the question of whether a single metric of "brain age" does justice to

the complex processes involved in brain development. In this talk, I will discuss the issues and challenges of developing a brain age model that is specifically tailored to adolescents and young adults. In particular, I will focus on the differences in interpretation of the brain age metric in young persons depending on whether it is an attempt to truthfully capture age-related brain patterns or to evaluate whether it has clinical relevance. Finally, I will present a methodological approach of training regional and/or modality-specific brain age models that may help tease apart or separate concepts of brain development and aging.

Lecture 2: *Brain Age in the era of deep learning and big data: Overfitting, specificity to disease, and the race for the wrong finish line*
Christos Davatzikos Presenter

The advent of complex machine learning methods, especially deep learning models which offer many degrees of freedom, along with large datasets for training such models, have set off a "race for the lowest MAE (mean absolute error)" in brain age models. This talk will discuss the pitfalls of this race, from the perspective of creating brain age models that are informative of brain pathologies. We show that tightly-fitting brain age models offer residuals that are not necessarily the best disease biomarkers, using a relatively current deep learning model trained on a dataset of over 10,000 individuals, and evaluated in the context of MCI, AD, schizophrenia, and depression. We discuss how simple principles explain why tightly-fitting, low-MAE, brain age models can be forced to focus on disease-irrelevant imaging features, hence providing disease-irrelevant residuals. We also discuss the value of orthogonalizing brain age models to disease-specific models. We suggest that brain age models need to be constructed and evaluated in relation to their goal, such as providing markers of advanced or delayed brain development and aging, or serving as markers of brain pathologies, rather than by means of their MAE.

Lecture 3: *Individual variations in brain age: Capturing ongoing brain change or reflecting early-life differences?*
Didac Vidal-Pineiro Presenter

Brain age delta is a very promising index of brain health in middle/older age proving valuable at predicting outcomes such as mortality or dementia. It is assumed, to some extent, that individual variations in brain age delta reflect ongoing and future neurobiological aging processes. Hence, it is common to interpret (higher) deltas as reflecting a steeper rate of brain aging and/or accelerated aging. A divergent interpretation argues brain age delta reflects constant, lifelong differences in brain structure associated with genetic and early-life factors. We tested whether brain age was related to faster brain aging, lifelong factors, or a combination of both. Specifically, if individual variations of delta reflect faster brain aging, (cross-sectional) brain age delta needs to be associated with measures of longitudinal brain change. If brain age delta largely captures stable differences in brain structure, it needs to relate to congenital factors assumed to be associated with constant, lifelong influences on brain structure such as birth weight and polygenic scores for brain structure. We tested these assumptions using two independent large test datasets (UK Biobank and Lifebrain) with >1300 individuals with longitudinal observations and brain age models based on T1-weighted features. The results showed very weak evidence of a relation between cross-sectional brain age and the rate of brain change measured longitudinally. Rather, brain age in middle and old adulthood was associated with the congenital factors of birth weight and polygenic scores of brain volume. The results suggest early brain development likely

has a strong effect on brain health throughout life and that T1-weighted-based brain age has low validity as a marker of ongoing within-person changes of the aging brain.

Lecture 4: *Beyond brain age prediction: Crosstalk between brain age and body age*
Ye Tian Presenter

Aging involves progressive, generalized deterioration and loss-of-function across multiple organ systems. Advanced aging is associated with increased risk of multi-morbidity of brain and body diseases. While the biological age of the brain is widely studied, the aging of other organs and systems is less well characterized and links between brain and body aging remain to be elucidated. In principle, biological age could be estimated in vivo for organs and body systems other than the brain, using organ-specific phenotypes. In this talk, I will show predictions of organ age using phenotypes specific to the brain and 7 body systems, including cardiovascular, pulmonary, musculoskeletal, immune, renal, hepatic and metabolic systems. This enables concurrent investigation of biological aging across the brain and the body. I will then present a multiorgan aging network, where an organ's biological age selectively and characteristically influences the aging of other brain and body systems. I will show unique multiorgan aging profiles for 16 chronic diseases, where advanced organ age extends from the organ of primary disease pathology to multiple systems. In particular, I will show evidence of advanced body age in people with common brain diseases and that advanced brain age is not only evident in major brain diseases such as multiple sclerosis, dementia, Parkinsonism and schizophrenia, but also prevalent in people with non-brain diseases such as diabetes, chronic kidney disease and chronic obstructive pulmonary disease. Finally, I will present several key modifiable environmental and lifestyle factors that may have the potential to slow brain and body aging.