The explanation of the bias in machine learning-informed brain age prediction from a perspective of brain resilience

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Introduction-BrainAGR

As people age, the brain changes with functional deterioration and increased risk of neurodegenerative diseases (1). However, does the degree of the brain aging is equal to chronological age? Not actually taking it-people's underlying senile proceedings would differ from their true age - an individual at the age of 70 may have the brain of an individual at the age of 75(2). This asynchronous change of brain is measured by an indicator – BrainAGE (3) (the difference between the brain age and the chorological age) which appears to reflect advanced or delayed brain aging. For a 70-year-old individual, BrainAGE = + 5, it means that the individual's brain age is 75-year-old. Studies have shown that lager positive BrainAGE is associated with faster physiological deterioration and even higher mortality (4). Many diseases not only limited in the field of neuropathy and psychosis such as HIV (5), chronic pain (6) and diabetes (7) have been showed to make the brain older. A more accuracy method to predict brain age based on neuroimaging data is fast becoming a key instrument in early warning of some diseases, evaluation of physiological conditions and to get the timely response treatment accordingly.

Brain Resilience

As a self-organized and adapted system, brain shows robustness in the gradual or sudden impairment processing. Complex maintenance, repair and compensatory mechanisms are labelled as resilience mechanisms tend to maintain the homeostasis of the brain. Therefore, significant individual variability could be observed in normal aging and even neurodegenerative diseases at different levels of brain pathology, physiology, and even damages or impairment (13).

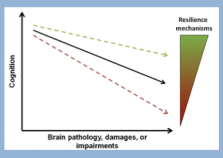

Fig. This association of the brain pathology, damages or impairments modulated by resilience mechanisms (13).

Fig. 1 Relationships among adverse (red), protective (blue), and mixed (purple) processes that culminate in signs and symptoms of neurodegenerative diseases （15）

Limitations-BrainAGE

With the advances of imaging and analytic techniques, the brain ageing could be predicted through modeling the trajectories of healthy brain at individual level. Currently, the cutting-edge methods of predicting brain age are machine learning-informed prediction, including support vector machine, random forest, Naive Bayesian algorithm and deep learning (8). Regard to the advances, one of the main future directions is to minimize the bias within the difference between the chronological age and predicted brain age (i.e., brainAGE) and further improve the estimation accuracy (9). In this literature review, a bias observed systematically underestimates the mean predicted brain age after 35 (10) The reason for this mean regression is generally considered to be the non-Gaussian distribution of subjects' age, but whether this explanation is an attribution error is not clear yet (9,11). The bias could lead to the unprecise brain-based interventions for the patients suffering from Alzheimer's disease and related dementias (ADRD).

Resilience and BrainAGE bias

A Possible explanation for the underestimation of brain age might be related to the brain resilience mechanisms. Neurocognitive and clinical impairments are associated with the exhaustion of network compensations. The preservation occurs continuously to maintain cognitive function by integrating the communications of specific brain regions (12). As a result, a person's brain age may differ from his or her chronological age. Among the brain regions, hippocampal volume, as a main resilience factor (13) may play a critical role in the prediction of brain age. However, after dimensionality reduction and multivariate associative techniques- Principal Component Analysis (PCA) and Canonical Correlation Analysis (CCA) tackling the high dimensionality of neuroimaging data, sufficient weight coefficient of hippocampal volume could not be ensured. The CCA loadings may provide a way to assess the contribution of each neuroimaging feature to age prediction (14). However, whether the BSR (bootstrapped ratio of CCA loading value) which evaluating contribution to age prediction from the statistical algorithm is consistent with the real aging changes is to be explored from the perspective of biological explain ability.

Positive BEainAGE factors:

AD
Traumatic brain injury
Schizophrenia
Epilepsy
Dementia
Down's syndrome
Prader-Willi syndrome
Common brain disorders
Chronic pain
HIV
Diabetes

Negative BeainAGE factors:

Influence of meditation
Education and physical exercise
Amateur musician

Negative BrainAGE and brain resilience

In the past studies, the exploration of brain resilience was limited to the physiological perspective. Negative BrainAGE value would be highly related to stronger brain resilience factors. The combination between the machine learning methods and physiological mechanisms provides a meaningful perspective to explore the brain resilience.
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