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Multi-Omics and Alzheimer's disease: a slower but surer path to an efficacious therapy?

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Alzheimer's disease (AD) is a slowly progressing neurodegenerative disorder of complex, and as yet uncertain, etiology. With a rapidly aging population in Western societies, AD poses a significant burden on resources. Because of the increasing threat it poses to healthcare system, AD has been a focus of intense investigations for last three decades. This has resulted in a fairly good understanding of the disease at cellular, genetic and pathological levels **(1)** and has yielded a number of experimental therapeutic drugs. Also, availability of large number of animal models has allowed for rapid testing of the potential therapeutic drugs. Unfortunately, despite their spectacular success in preclinical disease models, all of the potential drugs have failed in human trials **(2).**

Although the exact reasons for the failure is not known, new information from genetic, cell molecular and neuroimaging studies has started to shed some light on why the drug trials failed in humans. Findings from multiple investigations show that AD is a complex, multifactorial disorder and the late onset sporadic form of AD, which accounts for about 96-98% AD cases, results from a complex interaction of genes and environment with biological aging (indeed, aging is the most significant risk factor for developing AD). It is becoming increasingly clear that the prevailing view of the pathogenic mechanism of AD is oversimplified and provides at best, incomplete picture of the disease pathogenic mechanisms **(3)**. An emerging view of the disease **(Figure)** suggests that memory impairments and dementia results not as a linear consequence of an initial pathogenic event but rather through non-linear interactions that involve multiple brain cell populations (neurons, astrocytes and microglia), pathogenic forms of proteins tau and amyloid-beta, and altered signaling pathways as the brain *ages*. Healthy brain aging preserves these interactions causing only age-associated general decline in memory and cognitive function. By contrast, unhealthy aging causes dysbalanced interactions which impairs neuronal function and, thus, results in mild-cognitive impairment and eventually giving rise to AD **(4)**.

Not only do different types of brain cells (especially the microglia) play an important role in AD pathogenesis, unhealthy aging affects each cell type at multiple levels. Thus, harmful changes at epigenomic, transcriptomic, proteomic, metabolomic and lipidomic levels together result in neurodegeneration and give rise to AD. Therefore, a more complete understanding of the human disease can only be achieved through 'big data' composed of above-mentioned omics on blood, cerebrospinal fluid (CSF) and brain samples from autopsy materials. Luckily, development of large-scale omic platforms **(5)** and progress in various neuroimaging modalities **(6)** together with advances in bioinformatics and computational programming has already started to generate 'big-data' information from AD patients and age-matched healthy cohorts. The accompanying article by H. Zetterberg **(7), which is the first in a** Themed set of Reviews on "Omic and Systems Biology Approaches in Neurodegenerative Diseases" succinctly reviews the advances made in the field. The omic studies advance our knowledge of AD at multiple levels. These data help identify biomarkers that help in better disease diagnosis and help predict disease progression. More importantly, the omic data also helps in understanding the potential pathogenic mechanisms and therefore yield new and efficacious therapies.

While these investigations at the systems levels utilizing human samples will certainly advance our understanding of the disease and bring us closer to an effective treatment of AD, many challenges still remain. Perhaps, the most formidable challenge lies is in elucidating the biological meaning of various omic data. By its very nature, the omic data tend to be heterogeneous and show wide variability. Thus, many assumptions are made by statisticians to make the underlying biological trends visible. However, such assumptions can also lead to false biological interpretation. Therefore,

going forward, researchers who are comfortable with both biology and statistics will be required to identify and extract the correct biological meaning from the omic data. This will also require new statistical tools to analyze the data and identify the correct underlying biological information. However, ability to think in a non-linear manner while analyzing the omic data for biological relevance will be important since simulteneous interactions between scores of proteins, lipids and metabolites will rarely result in a simple deterministic outcome. Such fresh thinking will be the most crucial factor as the new biological insight is applied to conceptualize AD disease mechanism . Perhaps, lack of intellectual boldness and limited thinking may also have contributed to a string of failed clinical trials.

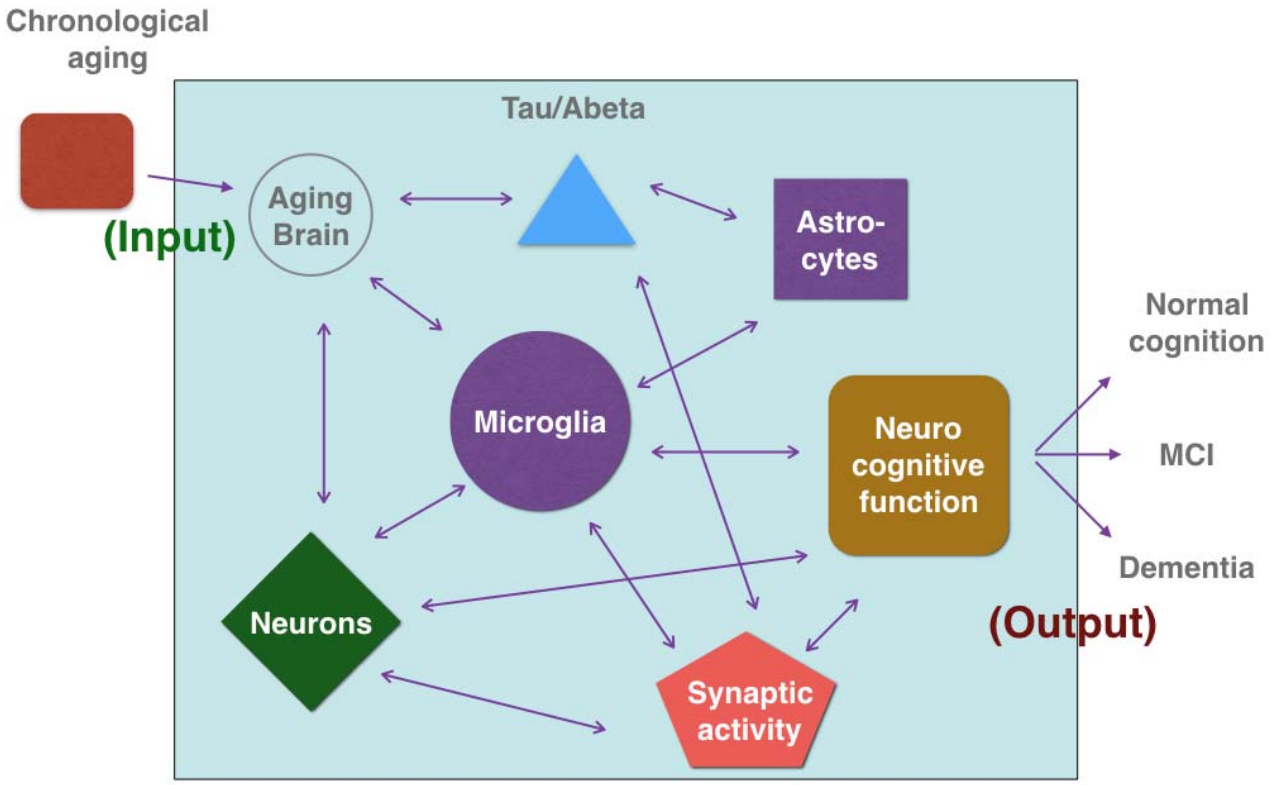

Figure. A schematic view of how brain aging regulates the non-linear interactions between various brain cell populations and pathogenic forms of tau and amyloid-beta proteins affecting synaptic activity and neurocognitive functions. Healthy brain aging preserve these physiological interactions and maintains normal cognition. However, these interactions become dysfunctional as a result of unhealthy brain aging, which impairs synaptic activity and neurocognitive function and ultimately leads to AD.

Bibliography:

1. Karch, C.M., C. Cruchaga, and A.M. Goate, *Alzheimer's disease genetics: from the bench to the clinic.* Neuron, 2014. **83**(1): p. 11-26.
2. Mehta D, Jackson R, Paul G, Shi J, Sabbagh M., *Why do trials for Alzheimer's disease drugs keep failing? A discontinued drug perspective for 2010-2015.* Expert Opin Investig Drugs, 2017 doi: 10.1080/13543784.2017.1323868.

3. Pimplikar SW, Nixon RA, Robakis NK, Shen J, Tsai LH., *Amyloid-independent mechanisms in Alzheimer's disease pathogenesis.* J Neurosci. 2010 Nov 10;30(45):14946-54.

4. Pimplikar SW, *Reassessing the amyloid cascade hypothesis of Alzheimer's disease.* Int J Biochem Cell Biol. 2009 Jun;41(6):1261-8.

5. Tosto G, Reitz C. Use of “omics” technologies to dissect neurologic disease. Handb Clin Neurol. 2016; 138: 91-106

6. Sharma SK, *Translational Multimodality Neuroimaging.* Curr Drug Targets. 2017 Mar 15 doi: 10.2174/1389450118666170315111542.

7. Zetterberg H. G, Reitz C. Use of “omics” technologies to dissect neurologic disease. Am J Physiol. 2017; this issue