Integrated Gene and Neuroimaging Brain Model Decodes Biological Mechanisms in Aging and Alzheimer's Disease

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INTRODUCTION

Both healthy aging and Alzheimer's disease (AD) are characterized by concurrent alterations in several biological factors. However, generative brain models of aging and AD are limited in incorporating the measures of these biological factors at different spatial resolutions. Here, we propose a personalized bottom-up spatiotemporal brain model which accounts for the direct interplay between hundreds of RNA transcripts and multiple macroscopic neuroimaging modalities (PET, MRI). **In normal elderly and AD participants, the model identifies top genes modulating tau and amyloid-β burdens, vascular flow, glucose metabolism, functional activity, and atrophy to drive cognitive decline.**

METHOD

1. From the Alzheimer's Disease Neuroimaging Initiative (ADNI) database, we pre-processed 6 longitudinal neuroimaging data (beta-amyloid and tau proteins, cerebral blood flow, glucose metabolism, R-fMRI, and grey matter volume) of 113 clinically stable healthy subjects (age = 73.7 ± 5.6 years, number of females = 59) and 129 diseased participants (age = 73.2 ± 7.1 years, number of females = 58) who were either diagnosed with AD (N = 35) at baseline or converted to AD (N = 94) after baseline diagnosis.
2. Using gene expression (GE) data of 6 neurotypical brains from Allen Human Brain Atlas, we derived brain-wide GE of 976 landmark genes with leading roles in central biological functions.
3. We developed a **novel mathematical model[1]** that incorporates: (i) disease- and aging-related longitudinal changes in neuroimaging data, (ii) GE-modulated interactions between the different neuroimaging modalities, (iii) propagation of alterations resulting from (ii) across brain networks.
4. Bayesian sparse linear regression with horseshoe hierarchy was used to solve the mathematical equation for each subject, where a regression coefficient represents the modulation effect of a gene on a particular neuroimaging modality (i.e., gene-imaging interaction).
5. By applying a multivariate singular value decomposition to evaluate the latent relationship between the gene-imaging interactions and slopes of five cognitive measures (MMSE, ADAS, executive function, memory score), we identified causal genes and pathways driving healthy aging and AD progression**. Please see Figure 1 for method overview.**

RESULTS

We identified 8 and 111 genes driving cognitive changes in healthy aging and AD, respectively (Figure 2). The biological factors (measured by imaging modalities) causally modulated by each gene, and factor alterations resulting from the modulation were also identified, e.g., our model revealed that APBB2 (amyloid beta A4 precursor protein-binding, family B, member 2) modulates glucose metabolism to cause longitudinal alteration of neuronal activity in AD. Pathway analysis of the identified genes suggested that AD and healthy aging share specific biological mechanisms, even though AD is a separate entity with considerably more altered pathways
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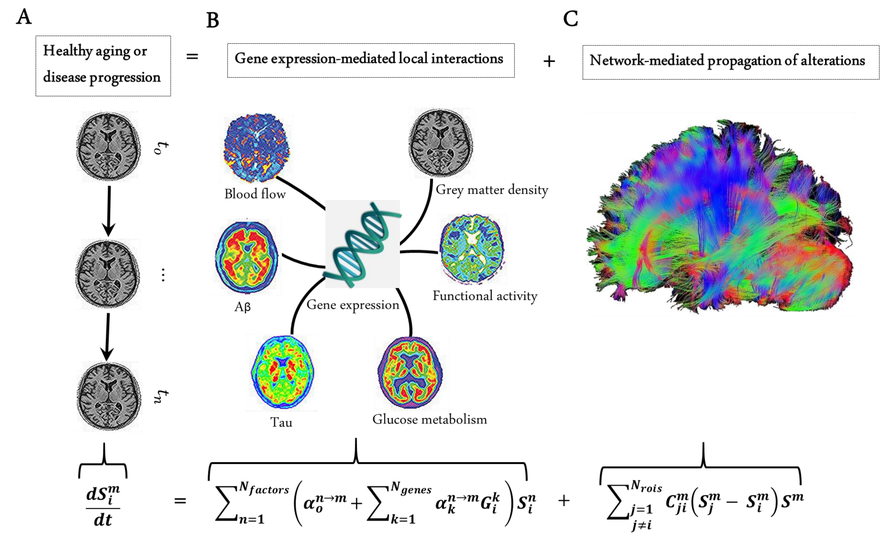

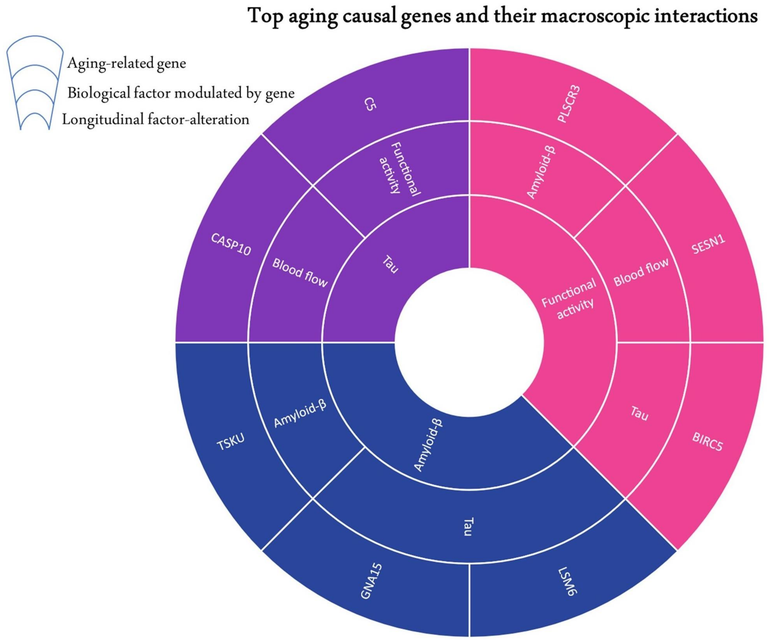

Figure 2. Top genetic determinants of multifactorial alterations in healthy aging. The innermost ring shows the longitudinal biological factor altered with aging, the middle ring displays the interacting biological factors driving the longitudinal alteration, and the outermost ring represents the causal genes modulating the interactions among biological factors (e.g., *SESN1* directly modulates blood flow to drive age-related alteration in neuronal activity).

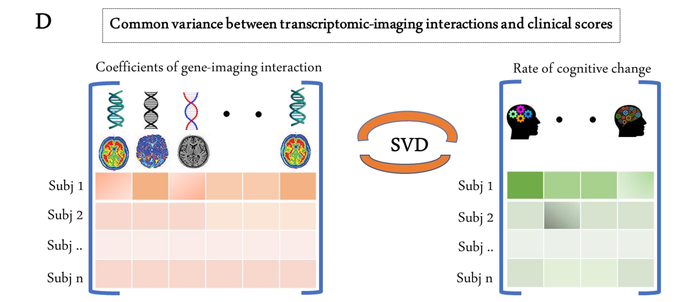

Figure 1: Modelling the gene-imaging interactions driving healthy aging and AD progression. **(A)** The longitudinal alteration of macroscopic biological factors in healthy and diseased brain due to gene-imaging interactions and the propagation of the ensuing alterations across brain network. **(B)** Regional multifactorial interactions between six macroscopic biological factors/imaging modalities are modulated by local gene expression. **(C)** Causal multifactorial propagation network capturing the interregional spread of biological factor alterations through physical connections. **(D)** By applying a multivariate analysis through singular value decomposition (SVD), the maximum cross-correlation between age-related changes in cognitive/clinical evaluation and the magnitude of genetic modulation of imaging modalities are determined in a cohort of stable healthy subjects (for healthy aging), mild cognitive impairment (MCI) converters, and Alzheimer's disease (AD) subjects (for AD progression). The key causal genes driving healthy aging and AD progression are identified through their absolute contributions to the explained common variance between the gene-imaging interactions and cognitive scores.

CONCLUSION

We developed a mathematical model to investigate the influence of gene expression on multifactorial alterations of biological processes in aging and AD progression. Our results are strongly consistent with previously reported studies and provided further insight into the molecular mechanism underlying healthy and pathological aging process. **Overall, this personalized model offers novel insights into the multiscale alterations in the elderly brain, with important implications for identifying effective genetic targets for extending healthy aging and treating AD progression.**

REFERENCES

1. Adewale, Q., Khan, A. F., Carbonell, F., & Iturria-Medina, Y. (2021). Integrated transcriptomic and neuroimaging brain model decodes biological mechanisms in aging and Alzheimer's disease. ELife, 10. https://doi.org/10.7554/eLife.62589

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