Investigating the ATN (Amyloid, Tau, Neurodegeneration) framework in Alzheimer's Disease and its causal genetic-drivers using Digital-Twins

Apoorva Bharthur Sanjay[1], Li Sun [1], Deepanshi Shokeen[1], Ole Isacson[2], So-Youn Shin[1] and Jeanne Latourelle[1]
(1) Aitia, Somerville, MA, USA (2) Harvard Medical School/McLean Hospital, Belmont, MA, USA

ALZHEIMER'S ASSOCIATION AAIC 24
#91647

Introduction

- **Amyloid, Tau and neurodegeneration (ATN), the hallmark pathologies of Alzheimer's Disease (AD) translating to measurable biomarkers are important for disease modifying therapeutics**
- **Using Aitia's AD Digital Twins, we explored the interconnection between these hallmark pathologies and their causal genetic drivers**

Methods

- AD Digital-Twins were built using AITIA's patented A.I. platform REFS™ [aitiabio.com], based on a Bayesian network model of data which reverse-engineered the connectivity of ~59K multi-modal variables and AD-related outcomes profiled from 317 subjects (Control:MCI:Dementia=97:191:29) from the ADNI consortium data (https://adni.loni.usc.edu)
- For ATN and cognition outcomes, we had the following measurements available

Category	Outcome measures
Amyloid	CSF abeta and Florbetapir (AV45) SUVR
Tau	CSF pTau
Neurodegeneration	Hippocampus volume, entorhinal thickness and FDG PET and CSF t-Tau
Cognition	mPACC TrailsB, mPACC digit, RAVLT and ADAS13

- The average causal effect of each upstream-downstream variables was estimated through *in-silico* counterfactual experiments:
  - To evaluate the temporal relationship between the ATN outcomes
  - To identify the causal gene-drivers (at blood RNA-expression level) of "ATN" outcomes
  - To investigate the known AD genotypic variants strongly driving ATN gene-drivers.
- Age-gene interaction was additionally explored through "double-intervention" experiments, to evaluate age-specific effects of gene-drivers on ATN outcomes.

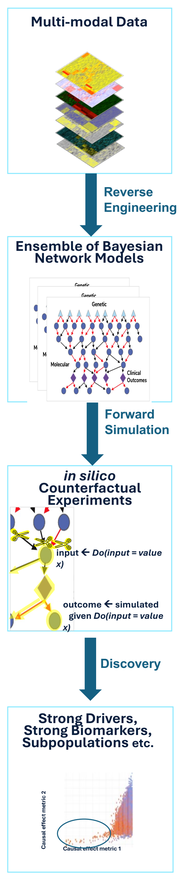
GEMINI Digital Twins Pipeline

Reverse Engineering

- Each *in silico* patient of the AD Digital Twins is comprised of an ensemble of Bayesian network models built from the training data using REFS™ causal AI platform [https://aitiabio.com].
- A Bayesian network model is a directed graphical representation of relationships between variables where each node is a variable, and each arrow is a conditional dependency.

Forward Simulation

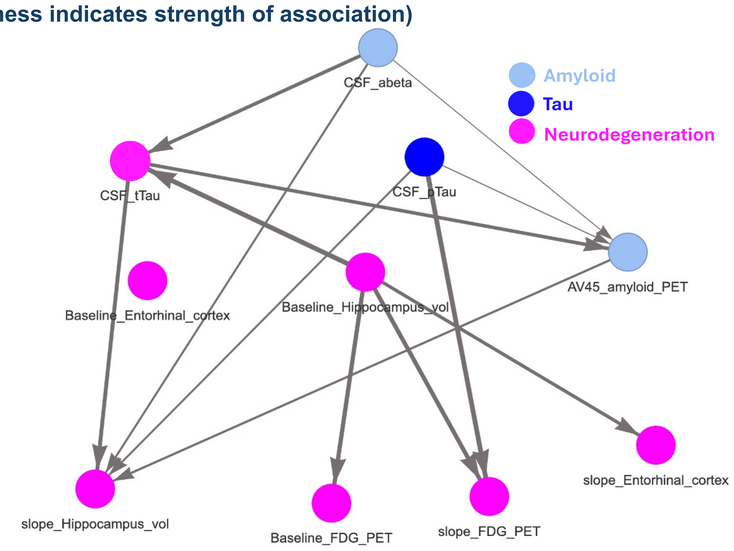
- Patient-level outcome values can be estimated in the AD Digital Twins, by *in silico* counterfactual experiments which computationally simulate patient outcome values through model interventions, known in causal inference as 'Do' operations.
- These estimations are done fully adjusting for any confounding effects identified in the causal models, which is necessary in causal inference as emphasized in randomized experiments.



Results

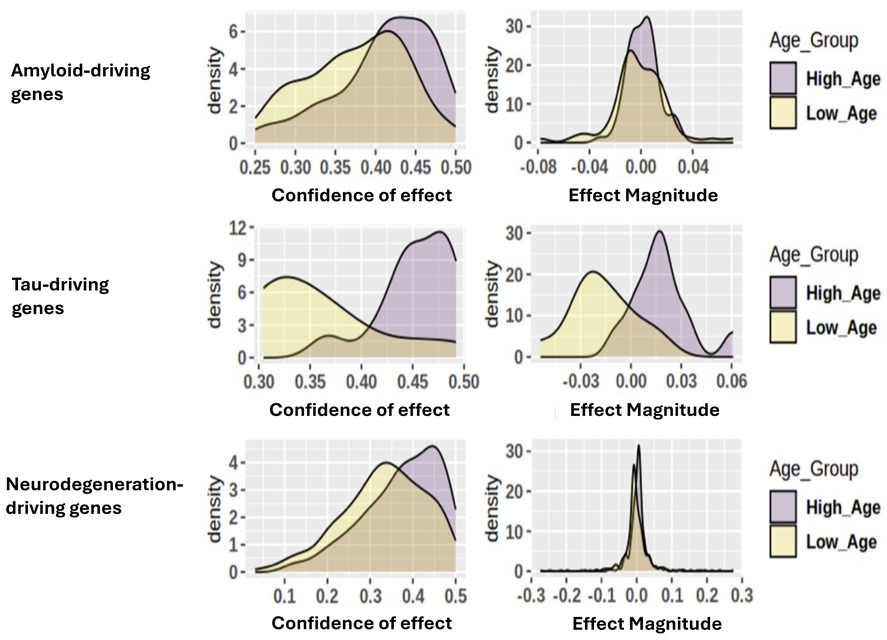
- **AD Digital-Twins evaluated the ATN temporal relationship, and recapitulated some known relationships such that CSF-abeta and Tau measures drive neurodegeneration measures [Figure-1]**
- **However, it also showed CSF-Tau measures to be upstream of amyloid PET, suggesting the total tau changes may interact with other outcome changes more dynamically over the course of disease progression**

Figure-1 : Schematic with ATN Temporal relationship (arrow indicates direction and thickness indicates strength of association)



- **For ATN-driving gene expressions, their age-specific effects on ATN outcomes were further estimated through double-intervention *in silico* experiments, and strong age-specific effects were observed especially for Tau-driving genes, where the effects showed the opposite directionality for younger vs older age groups**

Figure-3: Causal effect of ATN-driving genes on ATN outcomes estimated at High age (84 years old) and Low age (61 years old) corresponding to the 95th% and 5th % of the cohort age distribution.



- **Through *in silico* experiments, a total of 228 blood gene expressions driving ATN were identified, including 8 common ones [Figure-2 Left]**
  - **67 Amyloid driving-, 12 Tau driving-, and 207 Neurodegeneration driving-genes**
- **39% of these ATN-driving genes affected cognitive outcomes as well [Figure-2 Right], and were strongly related to immune-response and inflammation pathways in the Gene Set Enrichment Analysis**
- **These ATN-driving gene expressions were further investigated for their own drivers in the AD Digital-Twins, and multiple genetic variants were discovered. Many of these genetic variants were previously reported in AD GWAS, especially in the "NECTIN2" and "APOE" regions [Table 1]**
- **In addition, some Tau-driving genes were likely to be causally driven by Amyloid and Neurodegeneration driving genes**

Figure-2 : Number of gene expressions driving Amyloid, Tau and Neurodegeneration in the AD Digital-Twins

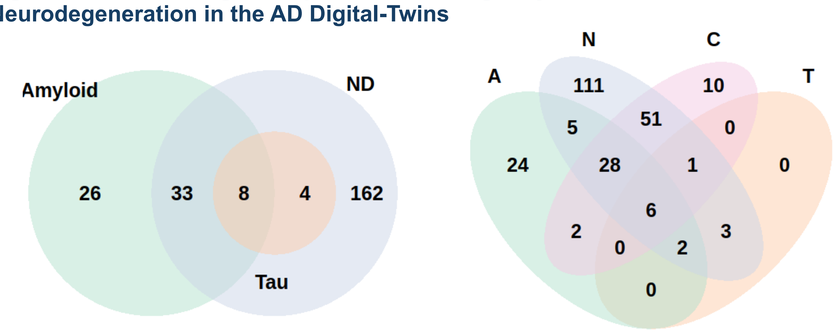


Table-1 : Known variants showing strong causal effect on genes driving Amyloid, Tau and Neurodegeneration outcomes(there were no variants specific to only Tau driving genes)

#Variant	Associated gene(s)	Category
rs10807828	NPVF, UBA52P1	Common to genes driving Amyloid, Tau and Neurodegeneration
rs11665676	NECTIN2	
rs117556552	ANO3	
rs17636071	SLC9A9	
rs17817600	PICALM	
rs433852	FAM83E	
rs59325138	APOE, APOC1	
rs7412	APOE	
rs157580	TOMM40	Specific to genes driving Amyloid
rs2965163	CEACAM16-AS1	
rs439401	APOE	
rs10501320	MADD	Specific to genes driving neurodegeneration
rs1081106	APOE	
rs12292911	PSMC3,RAPSN	
rs3740688	SPI1	
rs7185636	IQCK	
rs78986976	BCAM	
rs846858	IGSF23	
rs9381563	CD2AP-DT,B3GNTL1P2	

Conclusions

- **A.I. driven AD Digital-Twins recapitulated some known relationships of ATN, demonstrating that a-beta and tau levels (measured in CSF) drive neurodegeneration as measured by MRI and PET imaging**
- **It also identified tau-related abnormalities as likely early events in AD progression and more strongly linked to disease pathophysiology**
- **Aitia's Digital-Twins approach allows powerful and systematic evaluation of multiple modalities and outcomes, through causal inference and *in silico* counterfactual experiments, which will contribute to accelerating precision medicine efforts in AD**