Immune Signatures In Cytotoxic Lymphocytes Linked To Sleep Disturbances And Cognitive Decline In Early Alzheimer's Disease

Poster #7061 | P2-06

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Key Messages

Peripheral immune remodeling marks the transition from cognitive health -> mild cognitive impairment -> mild AD.

Immune-sleep-cognition axis: Peripheral immune changes are functionally linked to sleep and circadian disruptions.

T cell receptor repertoire contracts in mild cognitive impairment stage, and expands in mild AD.

Background

Alzheimer's Disease (AD) often presents with early changes in **sleep behavior** and **immune system dynamics** long before cognitive decline is evident. Recognizing these early indicators is crucial for timely diagnosis and intervention.

Aim

Understand the interplay between changes in the immune system, developing sleep disturbances and cognitive decline.

Data: ADIS study

"Early Diagnosis of Alzheimer's Disease by Immune Profiling of Cytotoxic Lymphocytes and Recording of Sleep Disturbances"

Duration: 07/2022 - 06/2025 | Funding: 1.3 Mio Euros by JPND Neurodegenerative Research

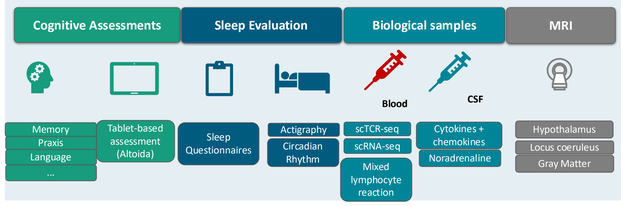
N= **79 participants**

- Mild cognitive impairment (MCI)
- Alzheimer's Disease (AD)
- Healthy Controls (HC)[

Positive AD CSF biomarkers

Table 1. Summary statistics of ADIS study participants.

	HC (n=26)	MCI-AD (n=25)	Dementia-AD (n=28)
Age	65,8±8,5	70,0±5,7	71,3±6,6
Age at onset	-	67,5±6,2	68,4±6,6
Sex (woman, %)	57,7	64	46,4
MMSE (scores 0-30)	27,1±1,7	24,4±2,7	22,1±3,3
Amnestic (%)	-	81	66

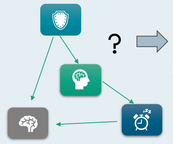


Methods

Disentangling connectivity between data modalities

- Score-based, continuous structure learning
- Gradient-based optimization with differentiable constraints

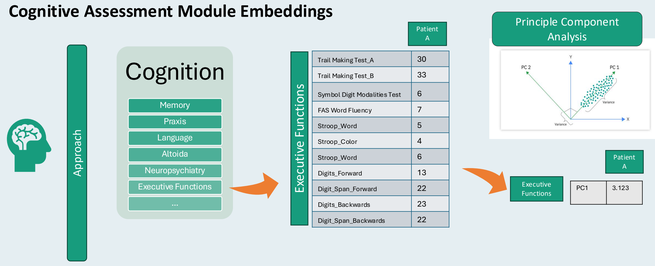
Approach: **D**irected **A**cyclic **G**raphs vi **M**-matrices for **A**cyclicity (**DAGMA**) (Bello et al., 2022, Advances in Neural Information Processing Systems).



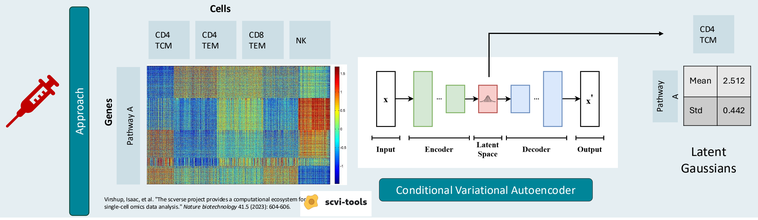
? Exploring the complex relationships among cognition, sleep and peripheral immune system changes

Machine learning approaches for low-dimensional embedding of high-dimensional data

Cognitive Assessment Module Embeddings



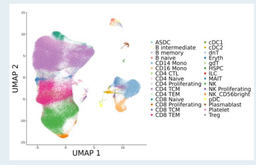
Immune Pathway Representations from Single-cell RNA Sequencing Data



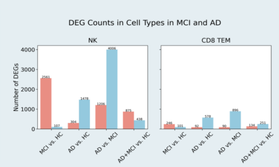
Virshup, Isaac, et al. "The scverse project provides a computational ecosystem for single-cell omics data analysis." *Nature biotechnology* 41.5 (2023): 604-606.

Results

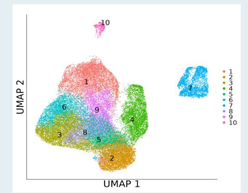
- Natural Killer cells and CD8+ T effector memory cells show the most prominent stage-specific transcriptional dysregulation.
- Clustering analysis reveals differential expression in CD8 T effector memory cells and Natural Killer cell populations, including signs of cellular senescence.
- T cell receptor repertoire contraction in MCI, reshaping and expansion in AD, indicating reduced clonal diversity on the prodromal phase.
- Sleep-immune-cognition axis revealed through directed acyclic graph learning.



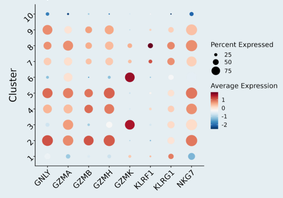
UMAP projection of single-cell RNA sequencing data of peripheral blood mononuclear cells from ADIS participants.



Differential gene expression counts in diagnostic stages of Natural Killer cells and CD8+ T effector memory cells.

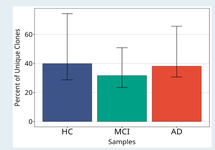


Leiden clustering of CD8+ T cell subpopulation.

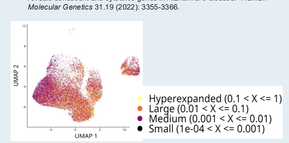


Cytotoxicity and senescence signature genes in CD8+ T cell clusters.

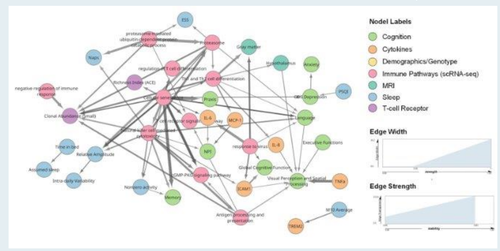
Dressman, Dallin, et al. "Genotype–phenotype correlation of T-cell subtypes reveals senescent and cytotoxic genes in Alzheimer's disease." *Human Molecular Genetics* 31.19 (2022): 3355-3366.



Number of unique clonotypes in healthy controls, MCI and mild AD.



Distribution of clonotype frequencies across clusters of CD8+ T effector memory cells.



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