

Identification of a blood metabolomic signature of cognitive aging

P1-15

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A signature of 70 metabolites (including lipids, amino acid derivatives and xenobiotics related to diet, gut microbiota, and environmental pollutants) was associated with global cognitive performances in two independant cohorts of older persons (N >2500). Two metabolite communities (PE/DAG lipids and secondary bile acids) showed a significant negative associations with cognition in both cohorts.

INTRODUCTION

Pathological cognitive aging is a heterogeneous process that can lead at neurodegenerative diseases such as dementia₁.
Novel untargeted high-throughput blood metabolomics approaches, that allows the agnostic quantification of thousands of metabolites, facilitating the identification of early risk factors and biological pathways leading to diseases₂.
Objective: Identify a robust metabolomic signature of cognitive performances in two population-based cohorts of older adults.

METHODS

Cohorts

B cube, Bordeaux (France), discovery
N=2,006 55-80 years at baseline, (2022-2025), 3-year follow-up ongoing
3C, Bordeaux (France), validation
N=9,294 65+ at baseline, inclusion in 1999, 17 years of follow-up

Metabolomic data

Untargeted metabolomics data are measured by LC/MS by Metabolon Inc. After pretreatment, 1,140 metabolites are selected (70% endogenous, 20% unannotated, 10% xenobiotics).

Cognitive data

A composite score of global cognition at baseline was built using a latent process mixed model₃ (B cube: 8 tests; 3C: 5 tests)

Statistical analysis

1. Metabolome structure (WGCNA)

2. Associations between metabolite communities and cognition

3. Metabolomic signature of cognition
Sparse Group LASSOs to select metabolites

4. Evaluate replication (3C)

RESULTS

Metabolomic signature

Signature of **70 metabolites** (>35.3% of bootstraps, AIC-based thresholding) :

- **26 endogenous compounds**
➔13 lipids, 6 amino acids, 3 peptides, 2 cofactors and vitamins, 1 energy-related metabolite and 1 carbohydrate
- **23 xenobiotics**
➔13 diet and gut microbiota related metabolites, 6 pollutants, 3 tobacco metabolites,1 drug metabolite
- **21 unannotated**
- **4 replicated metabolites:** PFOS (a PFAS), urolithin B glucuronide, resveratrol disulfate (1) (two polyphenol-derived compounds), and corticosterone (a hormone)
The **metabolomic signature score** was significantly associated with cognition in both cohorts ($\beta = 0.94$, 95%CI [0.81–1.07] and $\beta = 0.22$, 95%CI [0.00–0.44]).

CONCLUSION

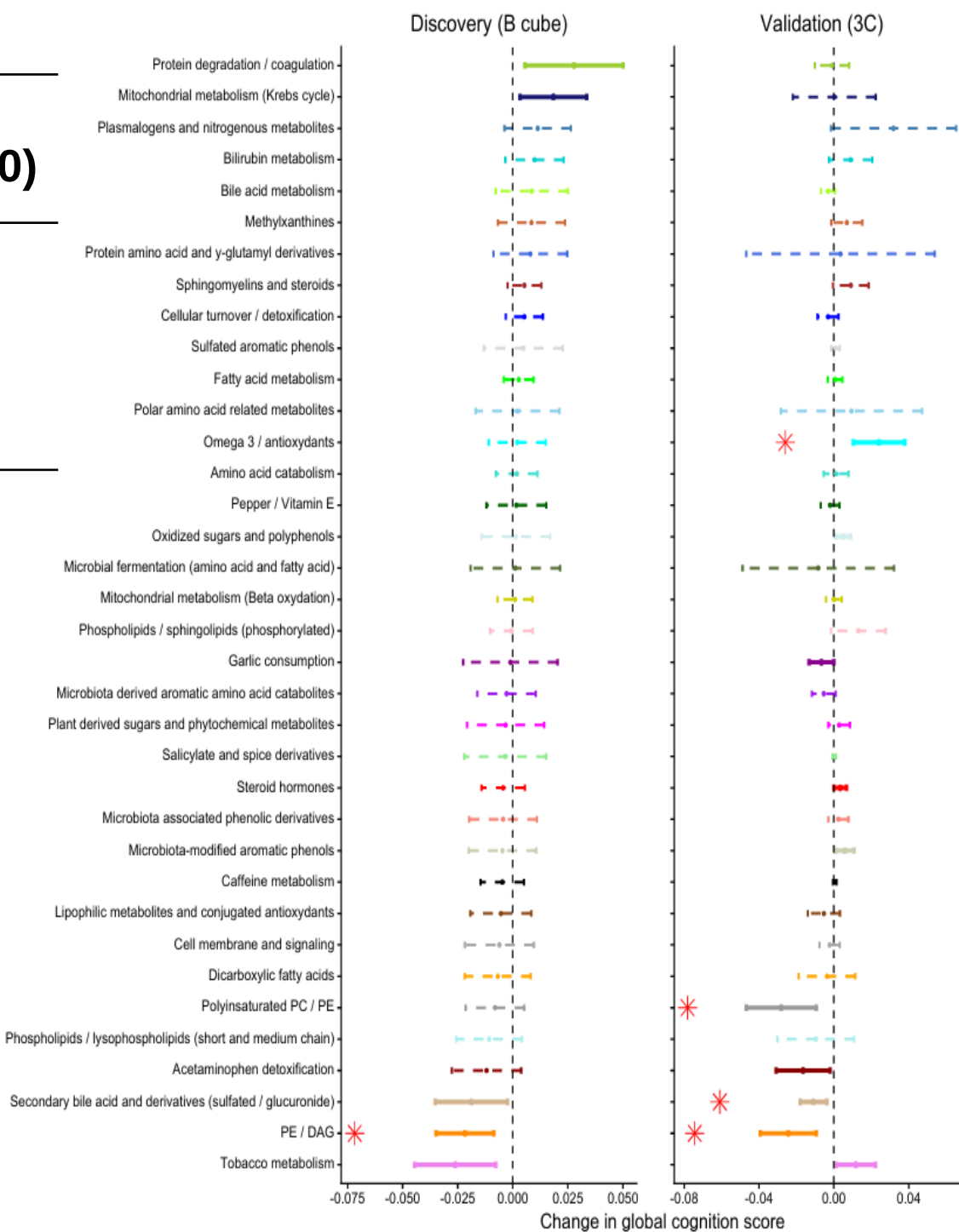
Cognitive function was associated with complex metabolic signatures encompassing both endogenous pathways (lipids, bile acids, and amino acids) and exogenous exposures, including diet-related metabolites and environmental pollutants. These findings suggest that an exposomic framework may provide valuable insights into the early determinants of cognitive aging.

Descriptive analysis

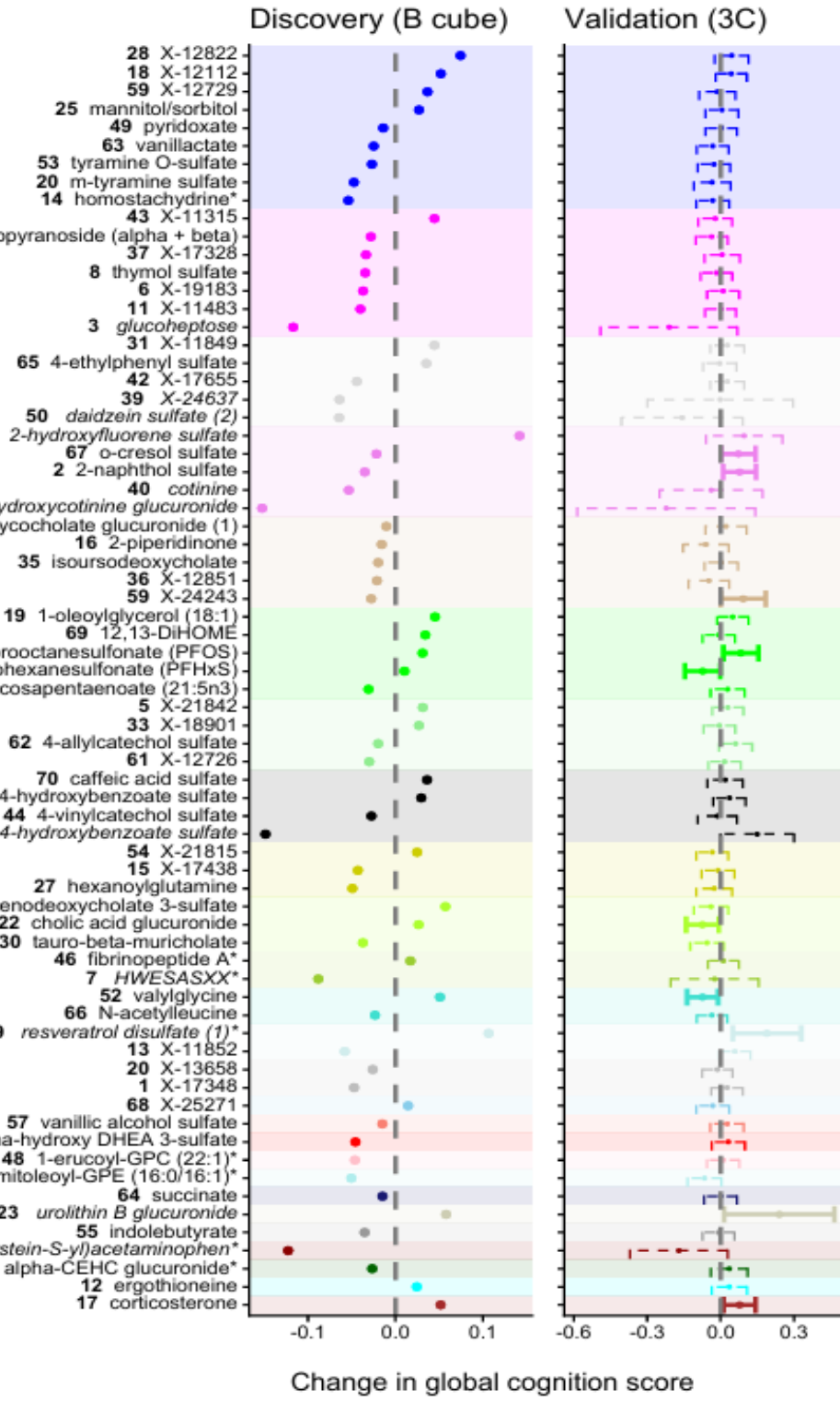
	B cube (N=1,627)	3C (N=1,040)
Age, mean	65.8	72.7
Sex, Female %	64.8	58.1
Education, University %	70.6	22.3

Association between metabolite communities and cognition

Two communities of **PE/DAG** and **secondary bile acid** showed a significant negative associations with cognition in both cohorts.



Forest plot of communities associations with cognition in both cohorts (Significant associations after multiple testing correction: red star)



Forest plot of association between the selected metabolites and cognition in both cohorts