

Multi-tissue metabolomic characterization of Alzheimer's disease identifies ammonia dysregulations in Alzheimer's disease

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Abstract

Although metabolic dysfunction is central to Alzheimer's disease (AD), its systemic manifestations remain poorly understood.

Using a large-scale platform across >1,000 individuals per tissue, we re- and meta-analyzed brain datasets, and generated cerebrospinal fluid (CSF) and plasma datasets. In pathology-confirmed AD and control, we identified **187, 92, and 494** altered metabolite levels in **brain, CSF, and plasma**, across 36 pathways. These metabolic changes were consistent across AD-related parameters, and some exhibited stage-dependency.

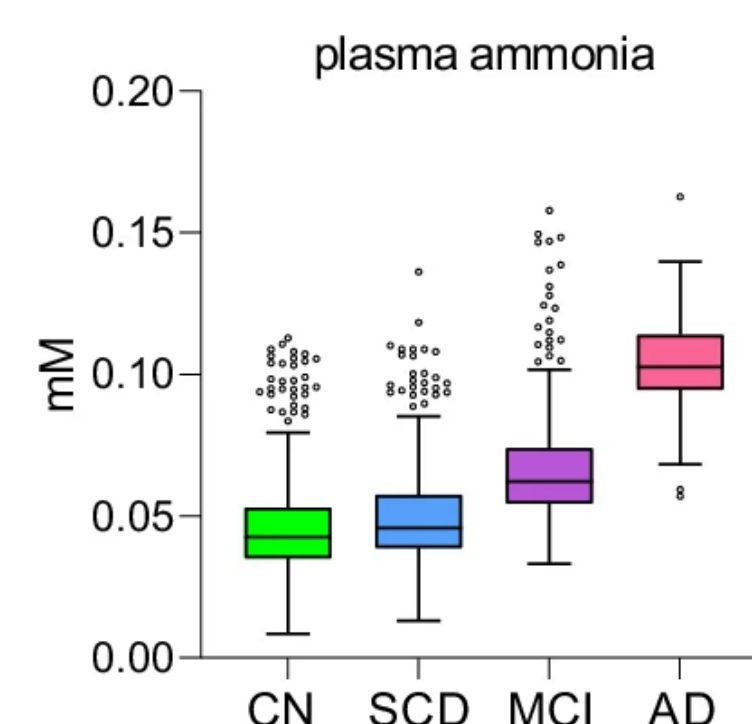
Early-stage dysregulation of urea cycle and gut aromatic amino acid (AA) metabolism increased peripheral ammonium, activating BCAA-supported glutamine synthesis. Early-stage asparagine synthesis in the brain protected against glutamine ammonia stress. Mid-stage AD brains showed partial urea cycle activation alongside reduced putrescine-to-GABA synthesis.

Background

High ammonia levels were found in the brain and CSF of AD. ARG2 is upregulated in the AD brain. (Al-Thani et al 2024 - review)

APP-Mice showed fully upregulated urea cycle in astrocyte, as well as downstream putrescine and GABA (Ju et al 2022)

Previously, blood metabolites have been proposed as AD biomarkers, including increased levels of ammonia (Chen et al 2024).



Objectives

Identify metabolite level changes in the AD brain, CSF, and plasma related to ammonia regulation
Determine the disease stage where these alterations occur

Method

We measured metabolomics using untargeted Metabolon-HD4 platform, and performed linear regression analysis comparing CO and AD, as well as each disease stage (CO A-T-, CO A+T-, MCI A+, AD A+T+)

Results

In the brain, altered metabolites were enriched for the urea cycle (UP), creatine metabolism (UP), and polyamine metabolism (DOWN).

In plasma, altered metabolites were enriched for the urea cycle (UP, tau & ptau driven)

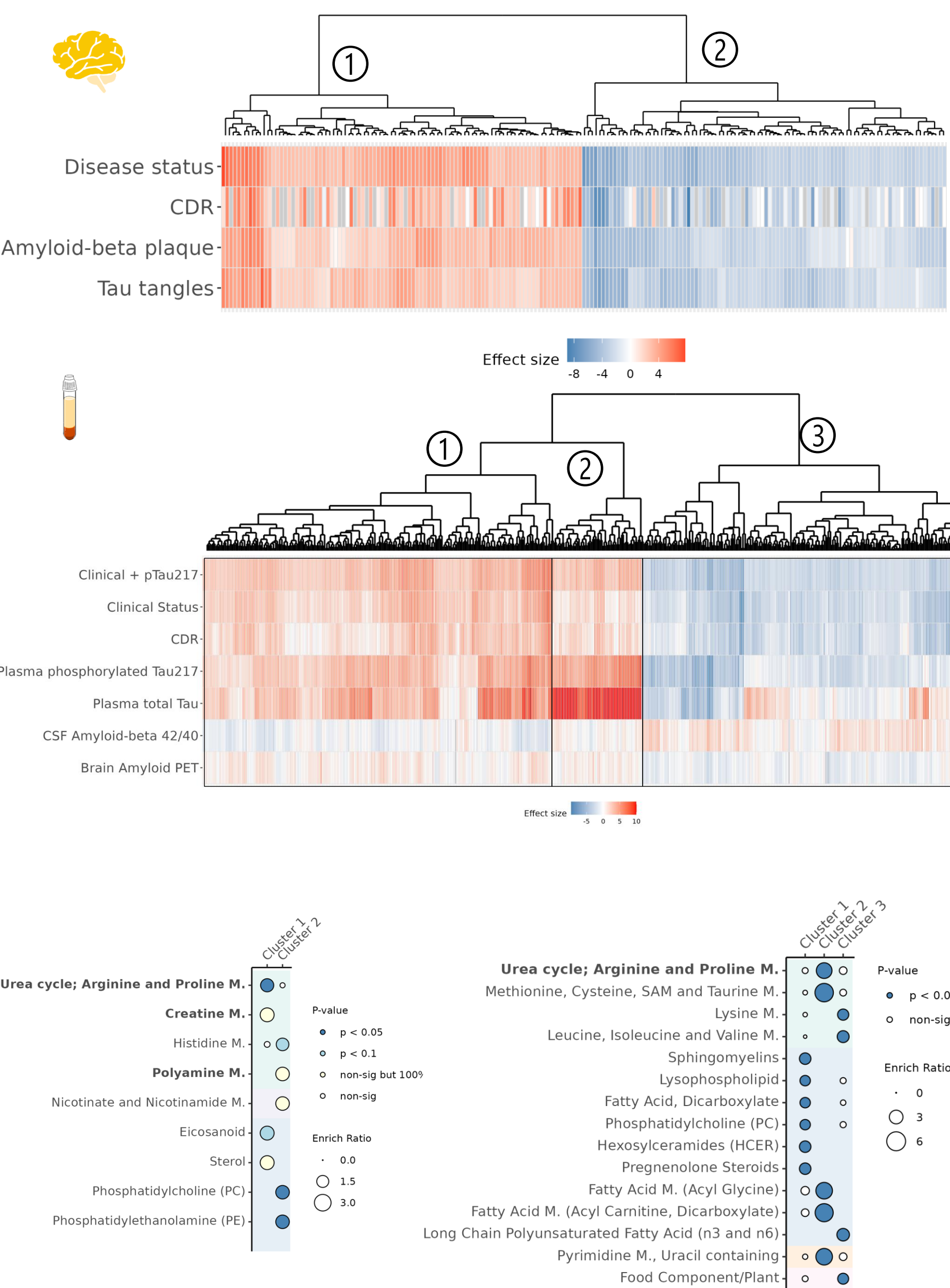


Figure 1. Metabolite associations with cognition and pathologies showed clusters enriched for various metabolic pathways

In the brain, mid-stage partially upregulated urea cycle, upregulated creatine synthesis, downregulated putrescine-GABA synthesis.

In plasma, early-stage dysregulated alternative urea cycle contribute to ammonia generation. Early-stage aromatic amino acid - indole synthesis generates ammonia. Early-stage peripheral detoxification through glutamine, depleting BCAAs.

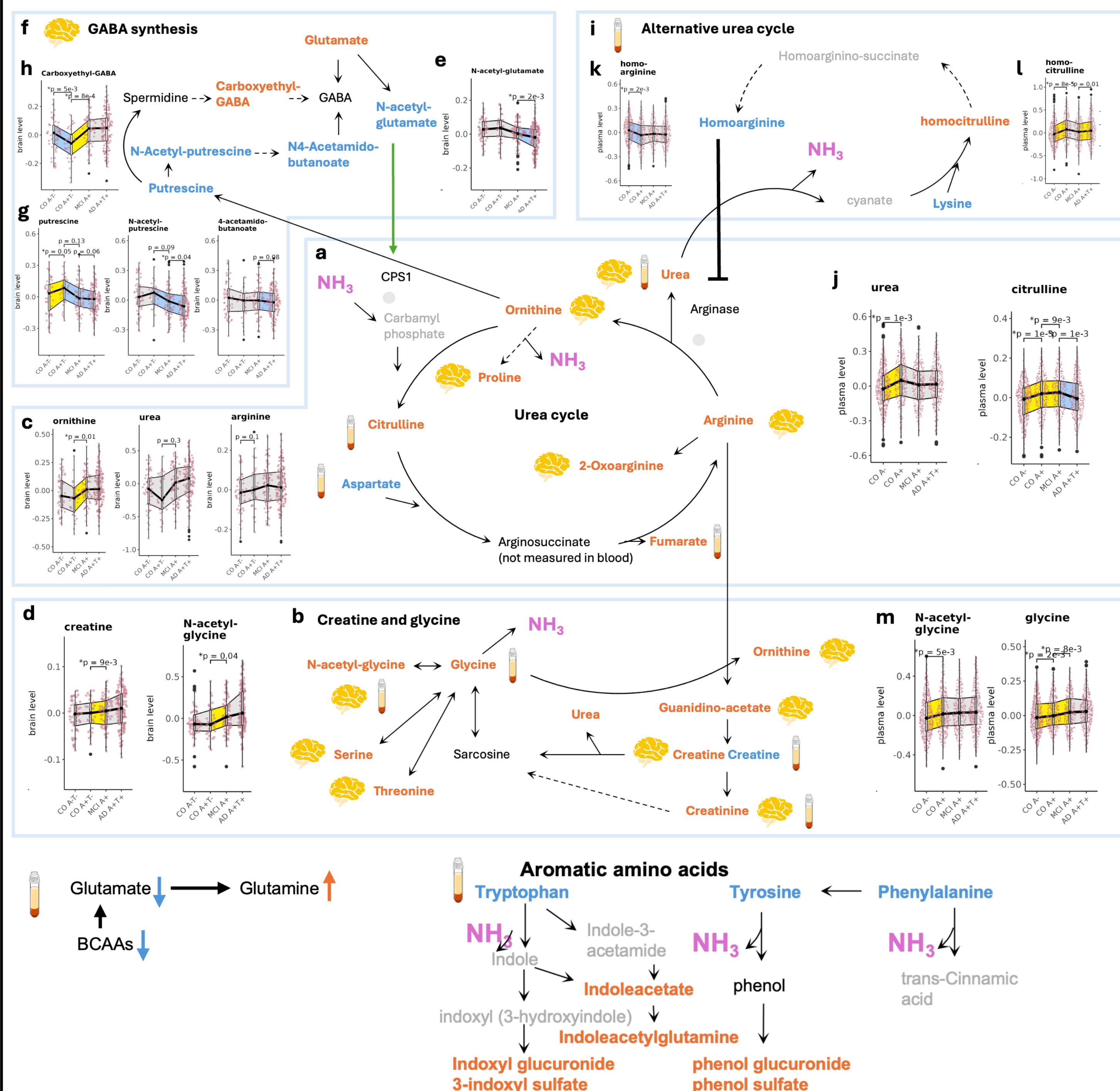


Figure 2. Metabolite changes related to ammonia generation and detoxification in brain and plasma of AD

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