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Interactions between brain and bile acid ratio profiles predict baseline cognitive status

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Abstract

Background: Alterations in the brain-gut microbiome system are thought to play an important role in the development of neurodegenerative diseases. While the great majority of secreted primary bile acids (BAs) are reabsorbed in the ileum, about 5% are metabolized by gut microbes and reabsorbed. Alterations in secondary BAs metabolism associated with specific gut-microbial species, and reflected in altered ratios of primary and secondary BAs have recently been linked with brain atrophy and cognitive decline. The aim of this study was to investigate whether interactions between brain-derived morphometric phenotypes and BA profiles can predict baseline cognitive status (cognitively normal (CN), mild cognitive impairment (MCI), Dementia (AD)) or conversion status (MCI to AD).

Method: The sample included 1013 CN, MCI, and AD participants from the Alzheimer's Disease Neuroimaging Initiative cohort. Regional brain morphometry was derived using Freesurfer v5.1 and Desikan-Killany atlas. Targeted metabolomics profiling quantifed concentrations of 20 BAs from serum samples. Analysis was performed using Data Integration Analysis for Biomarker discovery using Latent cOmponents (DIABLO). Data was split into a training and test sets (70/30 split) to determine predictive accuracy.

Result: A correlated brain and BA ratio signature predicted cognitive status (CN vs AD) with high predictive accuracy (see **Figure 1**). The brain signature of AD, compared to CN was characterized by gray matter atrophy in a limited number of regions including the hippocampus, entorhinal cortex, amygdala and medial temporal regions. The BA ratio signature was characterized by higher ratio of glycolithocholic acid and glycodeoxycholic acid to ursodeoxycholic acid, GLCA:UDCA, GDCA:UDCA along with a lower ratio of cholic acid to GLCA in AD. Predicted conversion from MCI to AD at 2 and 4 years had lower predictive accuracy (BER~ = 34%)

Conclusion: These findings demonstrate that interactions between brain signatures and secondary BA profiles predict baseline cognitive status with high accuracy. They

support the concept that differences in gut microbial metabolism of certain BAs, possibly related to diet, play a role in shaping the brain signature in AD patients. Compared to previously employed univariate approaches, the supervised multi-omics multivariate integration approach complements and elucidates the interactions along the brain gut microbiome axis that contribute to AD.

Figure 1.Correlated Brain and Bile Acid Ratios Signature Predicts Cognitive Status at Baseline with High Accuracy