



Microbiome-Metabolome-Neuropathology Profiling Identifies Systemic Metabolic Signatures in Early Neurodegeneration

Kang-Chen Fan^{1,2}, Cheng-Chin Kuo³, Yen-Ling Chiu⁴, Yi-Chien Liu⁵, Yi-Fang Chuang^{1,4}

¹ National Yang Ming Chiao Tung University, Taiwan ² National Taiwan University Hospital, Taiwan

³ National Health Research Institutes, Taiwan ⁴ Far Eastern Memorial Hospital, Taiwan ⁵ Cardinal Tien Hospital, Taiwan

ALZHEIMER'S ASSOCIATION

AAIC>26

Monday-0396 #11040

Introduction

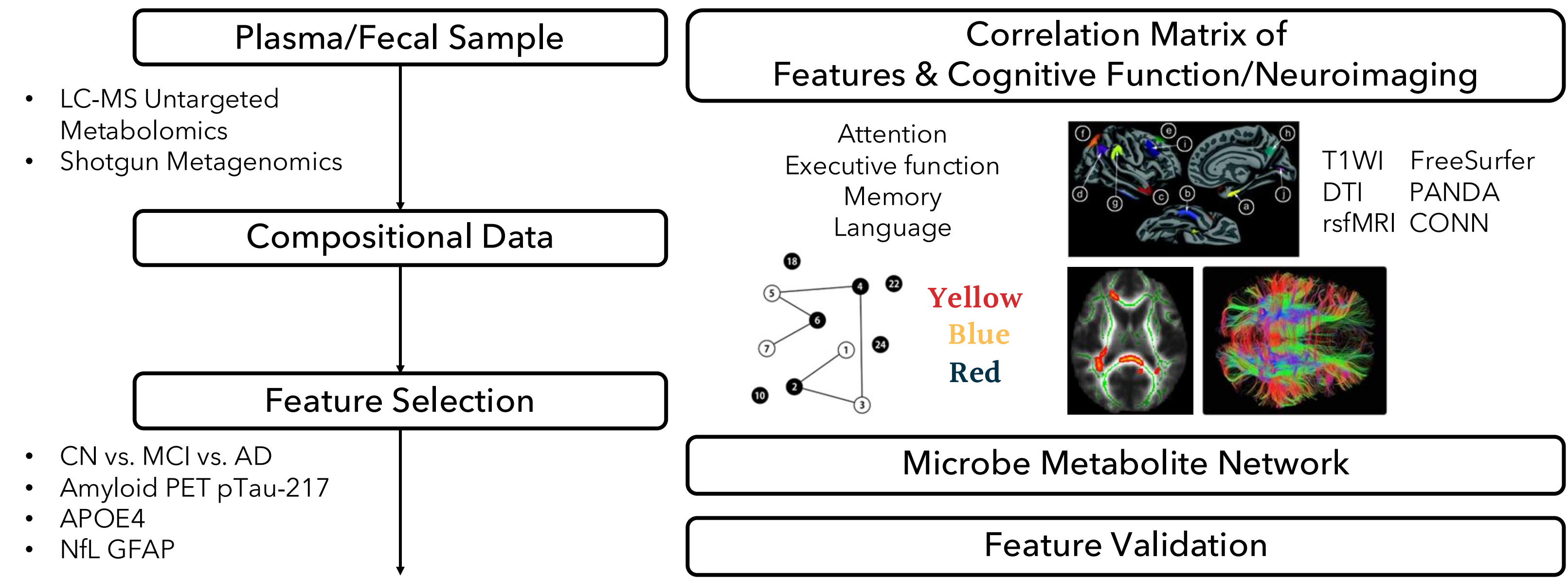
- Microbiota-gut-brain axis is a potential regulator of systemic homeostasis and may be implicated in Alzheimer's disease (AD) spectrum. [1]
- Unbiased "multi-"omics profiling is crucial for understanding host-microbial interactions that contribute to heterogeneous neurodegeneration, including those involved in producing bile acids, BCAAs, SCFAs, and TMAO. [2][3]
- However, current evidence is sensitivity to assumptions since most studies infer functional alterations from microbial composition rather than directly examining metabolome, the end product of both endogenous/exogenous cascades. [4]

BCAAs, branched-chain amino acids. SCFAs, short-chain fatty acids. TMAO, trimethylamine N-oxide.

Methods

Taiwan Precision Medicine Initiative on Cognitive Impairment and Dementia cohort (TPMIC)

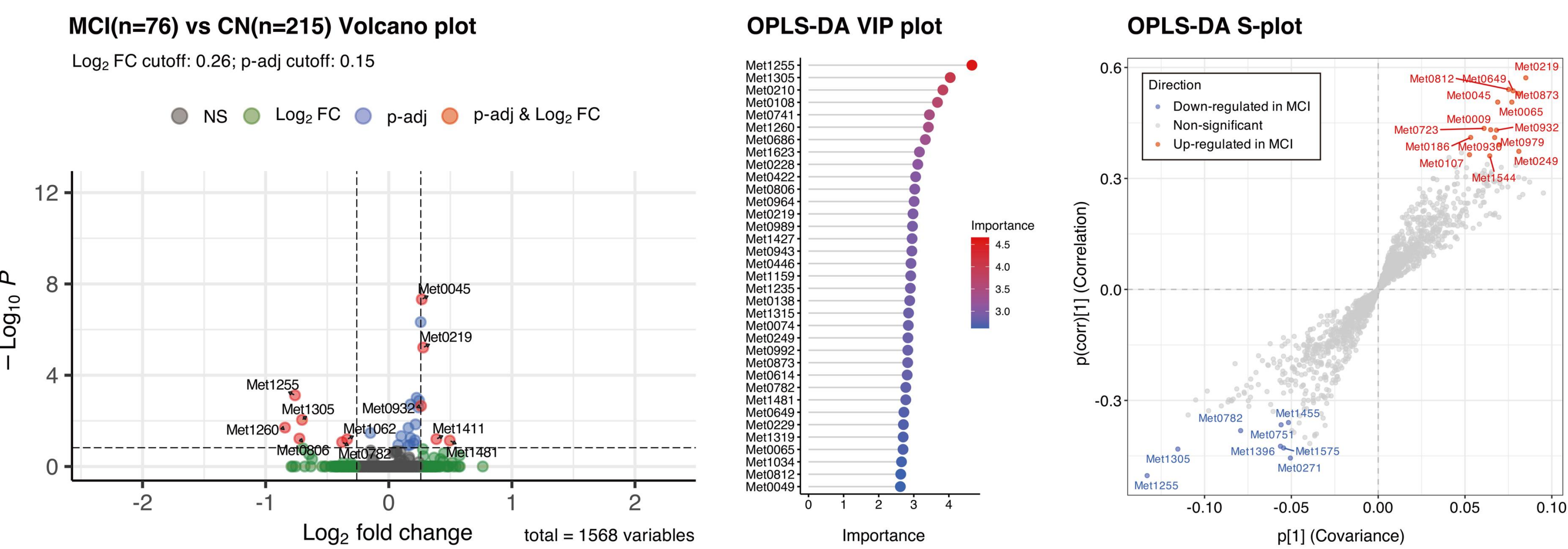
Characteristics	Cognitively Normal n = 215	Mild Cognitive Impairment n = 76	P
Age, years, mean ± SD	66.8 ± 6.5	72.9 ± 7.7	<0.001
Male, N(%)	78 (36)	30 (39)	0.62
Education, years, mean ± SD	12.6 ± 3.6	9.6 ± 4.4	<0.001
Smoking ever, N(%)	39 (19)	16 (22)	0.59
Drinking ever, N(%)	66 (32)	20 (27)	0.45
BMI, mean ± SD	24.7 ± 3.4	24.6 ± 3.9	0.81
Diabetes mellitus, N(%)	45 (22)	19 (26)	0.43
Hypertension, N(%)	76 (37)	34 (47)	0.14
MMSE, mean ± SD	28.2 ± 1.9	23.5 ± 5.0	<0.001



Conclusion

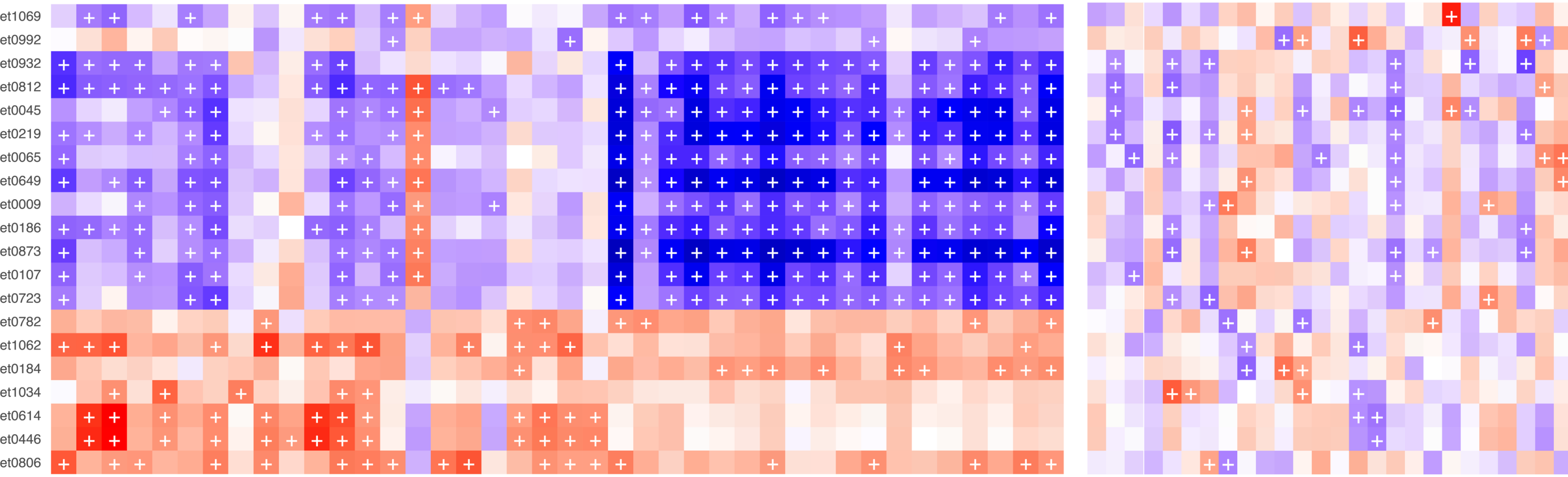
Our integrated profiling reveals that early neurodegeneration is characterized by a shift toward systemic metabolic dysregulation, potentially modulated by the gut microbiota. Discovery of metabolic markers of resilience highlights the importance of novel targets for preserving brain health. Future analyses with AD biomarkers will clarify the functional mechanisms in AD etiology.

Results



Met0806	2-Methylquinolin-4-ol	Met0723	4-Acetamidobutanoate	Met0219	N2-Dimethylguanosine
Met0446	Fusicoccin H	Met0107	Pirbuterol	Met0045	Thiodipropionic acid
Met0614	All-trans axerophthene	Met0873	1-Methylinosine	Met0812	2-Iodoheptadecanal
Met1034	(2E)-3-(2-Hydroxyphenyl)-2-propen-1-yl hydrogen sulfate	Met0186	NP-005146	Met0932	1-(2-Chlorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile
Met0184	NP-007994	Met0009	Valylproline	Met0992	(3a,5b,7a,12a)-24-[[Carboxymethyl]amino]-1,12-dihydroxy-24-oxocholan-3-yl-b-D-Glucopyranosiduronic acid (-)-Camphanic acid
Met1062	(±)-(2E)-Absciscic acid	Met0649	6-Methyl[1,2,4]triazolo[4,3-b]pyridazin-8-ol	Met1069	
Met0782	3-[[[2Z]-1-Oxo-2-buten-2-yl]pentanedioic acid	Met0065	Succinyladenosine		

Partial correlation matrix adjusted for age, gender, and educational years



+ unadjusted p-value < 0.05

LM, Logical Memory Test; DS, Digit Span; DSST, Digit Symbol Substitute Test; CTT, Color Trails Test; VF, Semantic Verbal Fluency; SCWT, Stroop Color and Word Test; BNT, Boston Naming Test; AD-CTS, AD cortical thickness score; CC, Corpus Callosum; FX, Fornix; TP, Tapetum; FMA, Forceps Major; CST, Corticospinal Tract; CR, Corona Radiata; ATR, Anterior Thalamic Radiation; PTR, Posterior Thalamic Radiation; IC, Internal Capsule; EC, External Capsule; CCG, Cingulum Cingulate Gyrus; CGH, Cingulum Hippocampus; SLF, Superior Longitudinal Fasciculus; ILF, Inferior Longitudinal Fasciculus; SFOF, Superior Fronto-occipital Fasciculus; IFOF, Inferior Fronto-occipital Fasciculus; UF, Uncinate Fasciculus; AD-WMIS, AD white matter integrity score

References

- [1] Loh, JS. et al. Microbiota-gut-brain axis and its therapeutic applications in neurodegenerative diseases. Signal Transduct. Target. Ther. (2024).
- [2] Batra, R. et al. The landscape of metabolic brain alterations in Alzheimer's disease. Alzheimer's & Dementia (2023).
- [3] Badhwar, AP. et al. A multiomics approach to heterogeneity in Alzheimer's disease: Focused review and roadmap. Brain (2020).
- [4] Bauermeister, A. et al. Mass spectrometry-based metabolomics in microbiome investigations. Nat. Rev. Microbiol (2021).

Contact



R⁶

vincentfan0105@gmail.com chuangy@nycu.edu.tw