

Metabolic Profiles Associated with Domain-Specific Cognition

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Introduction

- Data on metabolites associated with domain-specific change in cognition in cognitively normal adults remain limited.
- Understanding these associations may help elucidate early metabolic alterations linked to age-related cognitive trajectories.

Methods

- Study Sample**
- Washington Heights and Inwood Community Aging project (WHICAP) is a community-based cohort of multi-ethnic adults aged ≥65, designed to identify risk factors and biomarkers for aging and Alzheimer’s disease.
 - A random sample of 658 participants of WHICAP with available plasma for analysis were included in this study

- Data Collection**
- Metabolomics
- Plasma collected at baseline underwent untargeted liquid chromatography utilizing two chromatography columns and high-resolution mass spectrometry
 - Hydrophilic interaction column under positive ionization (HIL+)
 - C18 column under negative ionization (C18-)
 - Metabolite features were identified through unique M/Z ratio and retention time
 - Only metabolite features where >70% of samples had values above the detectable limit were used for analysis.
 - Prior to analysis, metabolite features were log transformed and standardized.
 - Metabolite features were annotated using an internal library and the human metabolome database (HMDB)

- Cognition
- Participants completed a comprehensive neuropsychological battery in their preferred language (English or Spanish)
 - Tests were summarized into four domains, memory, language, processing speed/attention, and visuospatial based on prior WHICAP confirmatory factor analysis and then z-scored.
 - For this cross-sectional analysis, we used the cognitive assessment closest to each participant’s blood draw with in one year.

Domain	Tests Included:
Memory	Immediate (SRT) Delayed (SRT) Recognition (SRT) Benton Visual Retention Test
Language	Naming (WAIS-revised) Letter Fluency (WAIS-revised) Category Fluency (WAIS-revised) Verbal Abstract Reasoning (WAIS-revised) Repetition and Comprehension (WAIS-revised) Boston Naming Test Controlled Word Association Boston Diagnostic Aphasia Examination
Processing Speed/Attention	Color Trails test 1 and 2
Visuospatial	Recognition and Matching trials from Benton Visual Retention Test Rosen Drawing Test Identities and Oddities Subset of Mattis Dementia Rating Scale

- Analysis**
- Multivariate regression was used to assess associations between individual metabolite features and domain-specific cognition at baseline (cross-sectional) adjusting for age, sex, education, and race.
 - P-values < 0.05 were considered statistically significant. Due to limited results after FDR adjustment, results for both nominal and FDR adjusted p-values are presented.
 - Metabolic pathways associated with the nominally significant metabolite features were identified using the Functional Analysis module in MetaboAnalyst.
 - Analyses were performed separately for memory, language, processing speed, and visuospatial cognition.

Results

Table 1. Study Sample Characteristics (N=658)		
	Mean or N	SD or %
Age	73.9	6.0
Education	11.0	5.5
Sex		
Female	449	68.2%
Male	209	31.8%
Race/Ethnicity		
White	147	22.3%
Black	159	24.2%
Hispanic	339	51.5%
Other	13	2.0%
Cognition Z-Scores		
Memory	0.469	0.756
Language	0.461	0.704
Visuospatial	0.421	0.624
Attention Speed	0.506	1.012

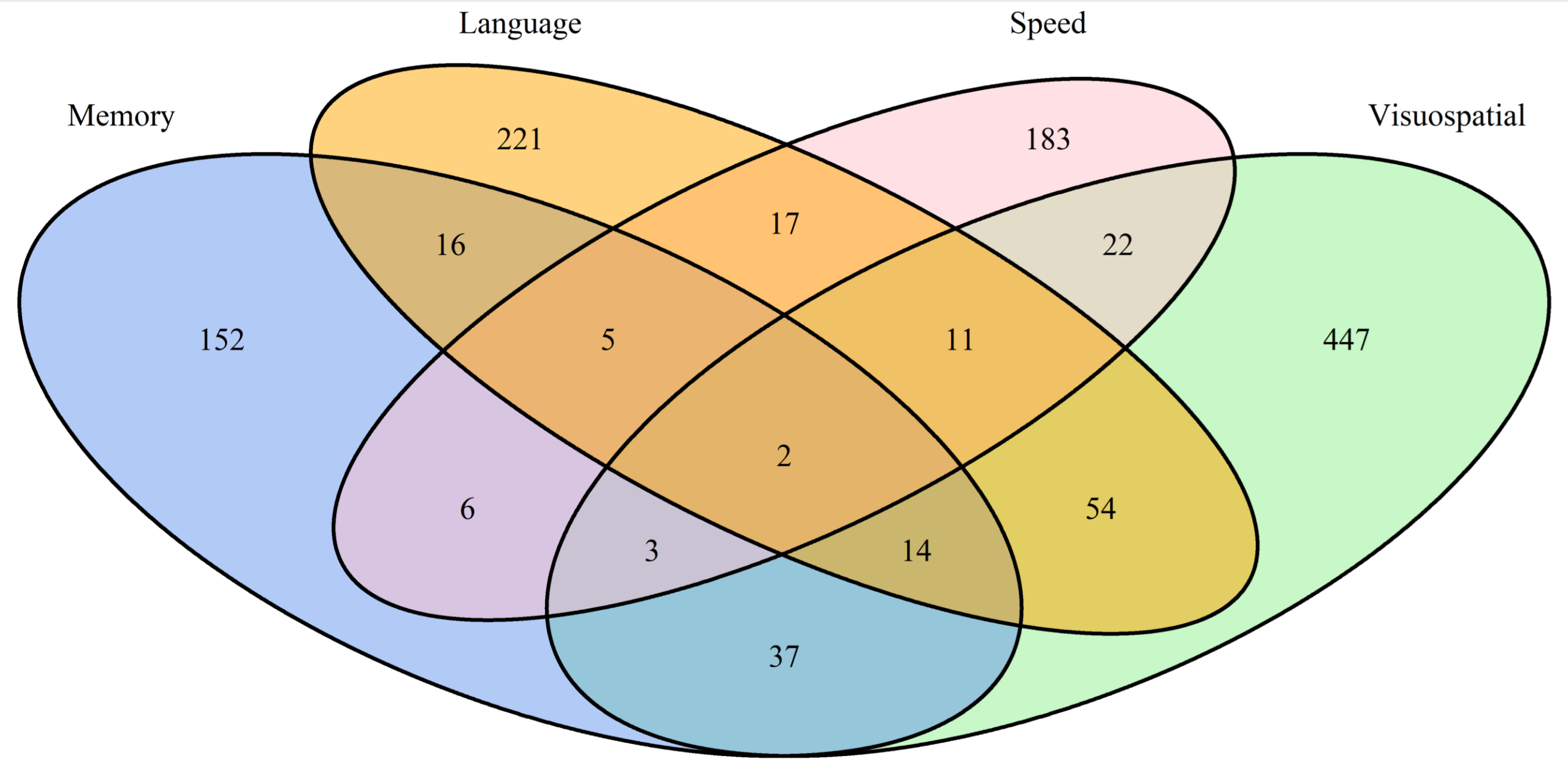
Table 2. Distribution of metabolite features by number of associated domains		
Domains	Number of Significant Metabolites	
	Nominal P-Value	FDR P-Value
Memory	235	0
Language	341	1
Speed	251	0
Visuospatial	591	0

- 5,741 metabolite features were detected in 70% or more of participants, and were included in this analysis
- After FDR adjustment, no metabolites remained significantly associated with domain specific cognition, with the exception of one metabolites with the language domain.
- The metabolite feature associated with language after FDR adjustment was annotated as several aromatic phenyl-containing compounds, including phenylpropanoid derivatives, aromatic, and multiple aromatic esters with the chemical formula of C₁₁H₁₄O₂

Table 3. Distribution of metabolite features by number of associated domains		
Number of Domains	Metabolite Features Associated	Percent
0	4546	79.2%
1	1008	17.6%
2	258	2.7%
3	32	0.6%
4	2	0.03%

One of which is annotated as SM(d18:114:0) with a chemical formula of C₃₇H₇₅N₂O₆P

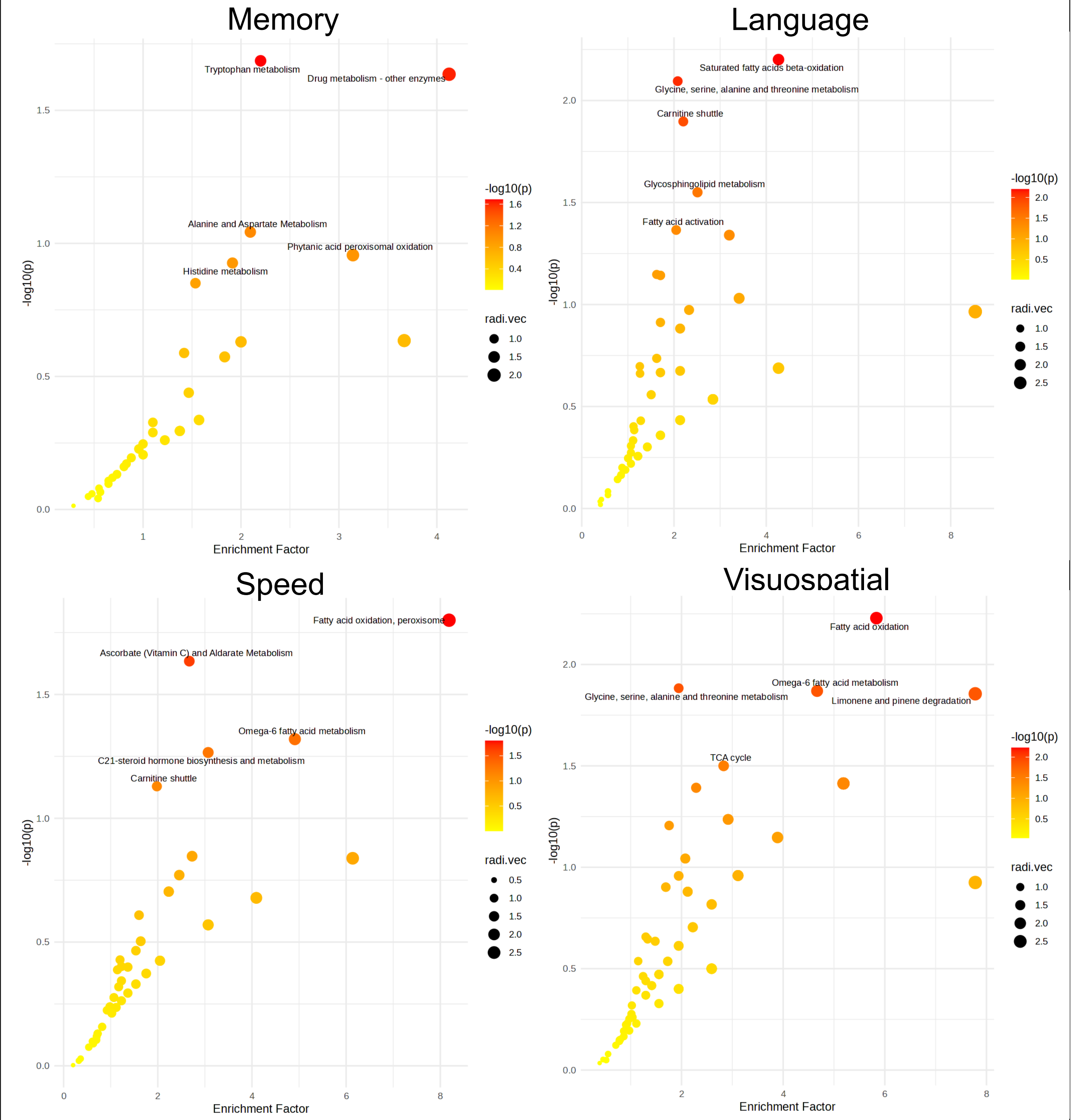
Figure 1. Overlap of nominally significant metabolite features associated with domains.



- No pathways were significantly associated with domain-specific cognition after FDR adjustment. Results presented are for nominally significant pathways.
- Lipid metabolism** was the most consistent biological process, with multiple pathways involving **fatty acid activation**, **β-oxidation**, **peroxisomal oxidation**, **omega-6 metabolism**, and **glycosphingolipid metabolism** enriched across domains.
- Energy metabolism** also appeared repeatedly, particularly for visuospatial function, through enrichment of the **TCA cycle**, **glycolysis/gluconeogenesis**, and **vitamin B1 metabolism**, all of which support mitochondrial energy production.
- Visuospatial performance** appeared to have the strongest metabolic signature, with enrichment spanning lipid, carbohydrate, and mitochondrial energy pathways.

Table 4. Functional analysis identifying enriched metabolic pathways among nominally significant metabolite features				
Pathway	Memory	Language	Speed	Visuospatial
Ascorbate (Vitamin C) and Aldarate Metabolism			*	
Biopterin metabolism		*		
Carnitine shuttle		*		
Drug metabolism - other enzymes	*			
Fatty acid activation		*		
Fatty acid oxidation				*
Fatty acid oxidation, peroxisome			*	*
Glycine, serine, alanine and threonine metabolism		*		*
Glycolysis and Gluconeogenesis				*
Glycosphingolipid biosynthesis - ganglioseries				*
Glycosphingolipid metabolism		*		
Limonene and pinene degradation				*
Omega-6 fatty acid metabolism			*	*
Saturated fatty acids beta-oxidation		*		
TCA cycle				*
Tryptophan metabolism	*			
Vitamin B1 (thiamin) metabolism				*

* P-value<0.05
Figure 2. Summary of metabolic pathways identified by functional analysis across cognitive domains.



Conclusions

- Distinct metabolomic profiles were observed across cognitive domains, with limited overlap in associated metabolite features.
- Visuospatial performance demonstrated the largest number of unique metabolite associations.
- Functional analyses consistently implicated lipid, energy, and amino acid metabolic pathways across cognitive domains.
- Only one metabolite feature remained significant after FDR correction, emphasizing the exploratory nature of the pathway findings.
- These results identify candidate metabolic pathways that warrant validation in larger, independent cohorts.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.