

BCAN-Mediated Extracellular Matrix Remodeling Links Type 2 Diabetes to Alzheimer's Disease

A multi-omics machine learning and mediation analysis framework with planned experimental validation

Authors: to be added | Affiliations: to be added | Contact: to be added

Central message

Hyperglycemia-associated BCAN loss may represent a brain-ECM pathway connecting T2D to AD pathology.

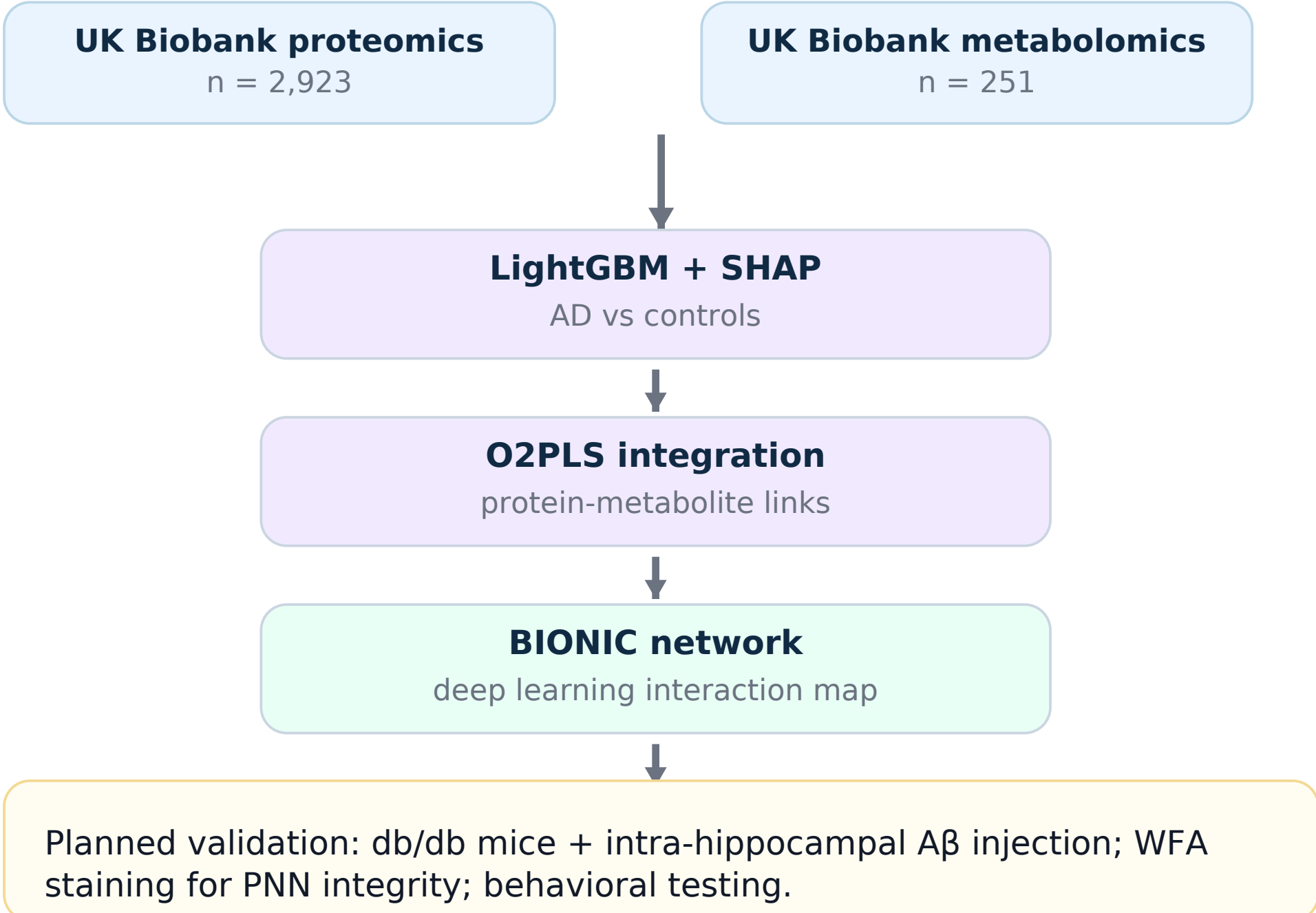
1. Background & Hypothesis

Clinical premise. Epidemiological evidence indicates that Type 2 Diabetes (T2D) is associated with increased Alzheimer's disease (AD) risk, but the molecular bridge remains incompletely defined.

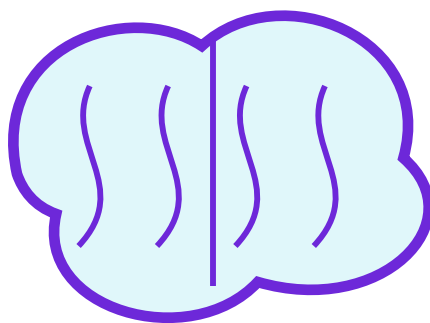
Hypothesis. Chronic high glucose remodels the neuronal extracellular matrix through brevican (BCAN), weakening perineuronal nets and promoting synaptic instability.



2. Cohort & Analytical Workflow



3. Why BCAN?



BCAN (brevican) is a brain-enriched extracellular matrix proteoglycan involved in synaptic microenvironment organization and perineuronal net biology.

- Biological plausibility: ECM remodeling provides a direct route from metabolic stress to neuronal circuit vulnerability.
- Omics signal: BCAN emerged from protein-metabolite integration rather than single-feature screening alone.
- Testable mechanism: BCAN loss can be evaluated through PNN integrity and behavior in diabetic AD-like mice.

4. Key Results

Top multi-omics candidate BCAN

Brain-specific ECM protein prioritized as a bridge between metabolic features and AD.

Model performance AUC 0.87

LightGBM distinguished AD cases from controls using proteomic/metabolomic features.

Metabolic association

Glucose ↓ BCAN

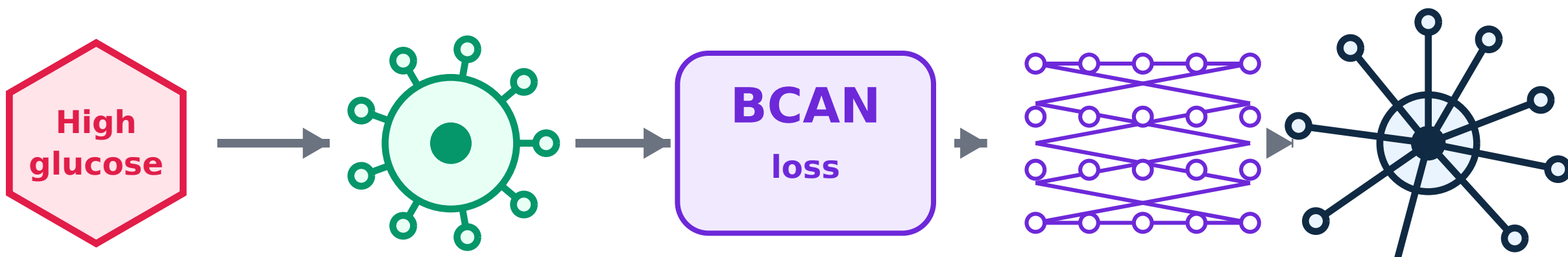
Plasma glucose showed a negative association with BCAN expression.

Mediation signal

5.8%

BCAN mediated part of the T2D-AD association; indirect effect = 0.001, $P < 0.001$.

5. Proposed Mechanistic Model



Interpretation: The data support a model in which metabolic dysregulation does not act only through systemic insulin resistance or inflammation. Instead, hyperglycemia may converge on the neuronal extracellular matrix, with BCAN downregulation destabilizing PNNs and thereby lowering synaptic resilience.



6. Statistical & Network Integration

SHAP prioritization

Ranks features contributing to AD-control discrimination; emphasizes interpretability rather than black-box ranking.

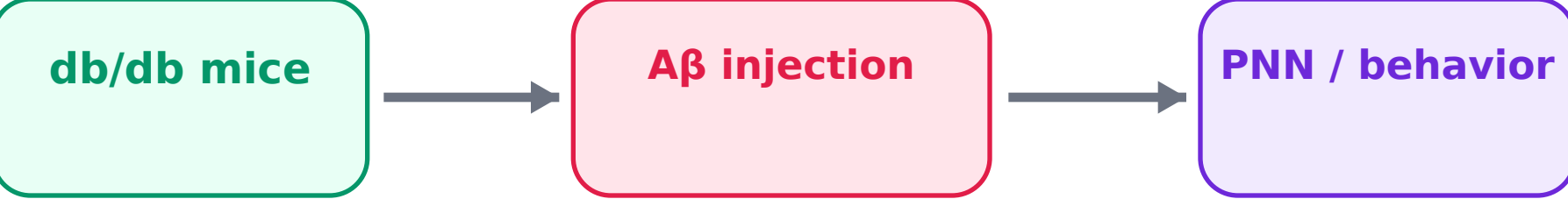
O2PLS coupling

Separates shared protein-metabolite structure from modality-specific noise to identify cross-omics associations.

BIONIC network

Integrates biological interaction layers using deep learning to infer candidate network neighborhoods around BCAN.

7. Planned Experimental Validation



- PNN integrity: WFA staining in hippocampal regions.
- AD-like injury: intra-hippocampal Aβ challenge.
- Functional readout: behavioral testing to link ECM damage with cognition.

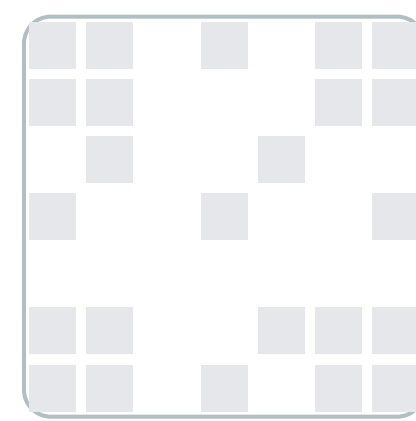
8. Conclusions

- BCAN is a high-priority candidate linking metabolic dysregulation to AD in the multi-omics framework.
- Hyperglycemia-BCAN-PNN provides a mechanistically testable ECM route from T2D to neurodegeneration.
- Mediation effect is modest but significant, suggesting BCAN is one component of a broader metabolic-neurodegenerative axis.
- Next step: validate whether BCAN/PNN loss is causal in diabetic AD-like models.

9. Limitations & Cautions

- Plasma omics may not fully capture central nervous system ECM remodeling.
- The BCAN-mediated proportion of the T2D-AD effect is partial, not a complete explanation.
- Experimental validation is designed/planned; mechanistic causality remains to be demonstrated.
- Replication in independent cohorts and brain-region-specific datasets will strengthen inference.

10. Poster Information



QR placeholder

Add before printing: abstract ID, presenting author, author affiliations, institutional logos, funding, conflicts of interest, and data/code link if available.

Suggested keywords: Type 2 diabetes; Alzheimer's disease; BCAN; extracellular matrix; perineuronal nets; multi-omics; mediation analysis.