Brain-Derived Exosome Biomarkers Identify Low Cognitive Performance After Traumatic Brain Injury in Service Members and Veterans

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Non-disclosures

- Katie Edwards, PhD, RN has no conflicts to report

Learning Objectives

- Describe the potential role of brain-derived exosomes as biomarkers of cognitive performance after traumatic brain injury (TBI).
- Identify key biological processes that may contribute to post-TBI cognitive performance, including neuroinflammation, neuronal dysfunction, and neurovascular injury.
- Explain how brain-derived exosome biomarkers could support earlier risk stratification and intervention strategies in service members and veterans with TBI.

Background

- Persistent cognitive dysfunction is common following TBI, yet the biological mechanisms underlying variability in cognitive outcomes remain incompletely understood.
- Brain-derived exosomes carry proteins reflective of neuronal and microglial activity.
- Characterizing exosomal protein signatures may identify biological pathways associated with cognitive performance after TBI.

Brain-derived exosomes

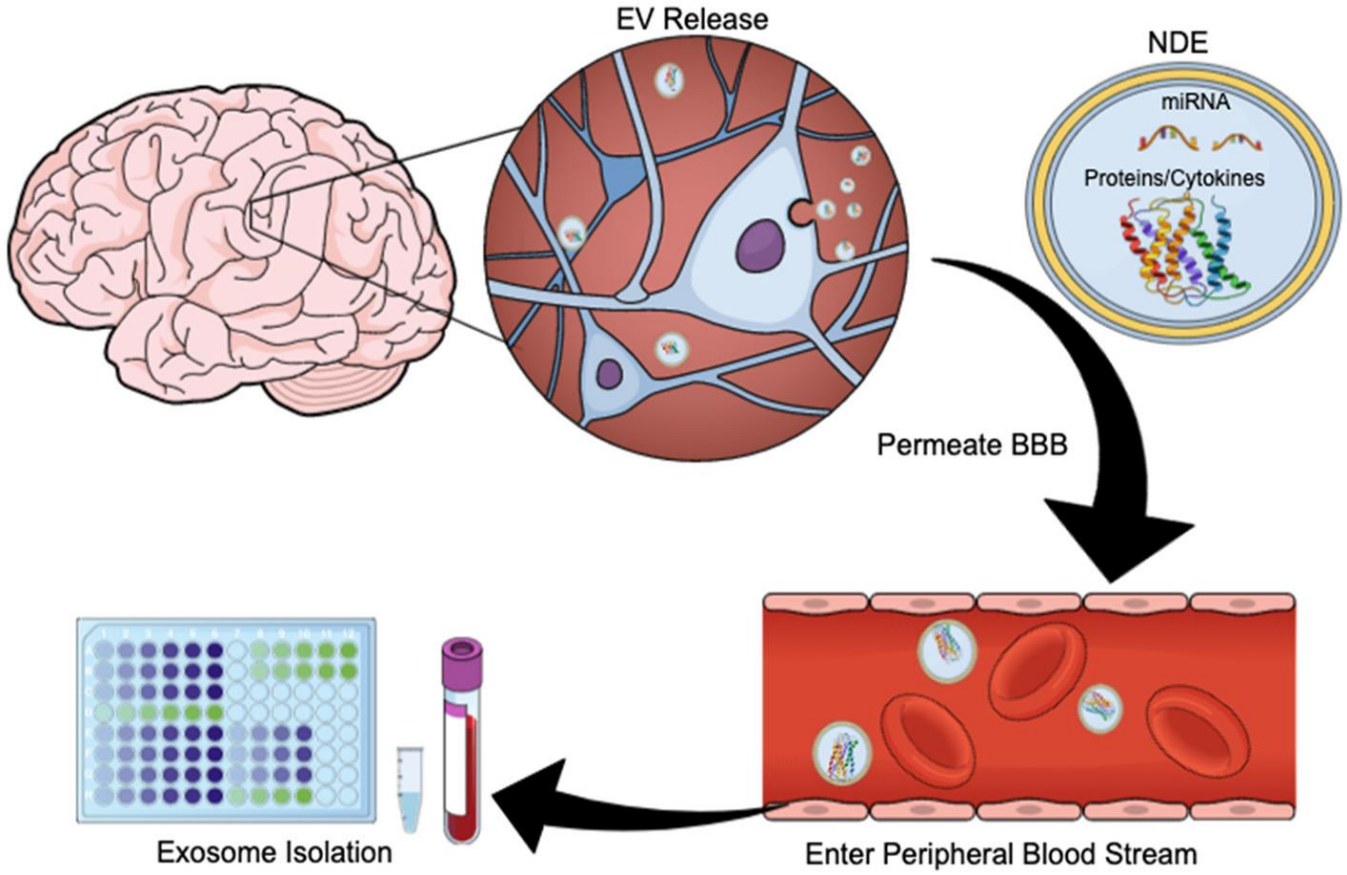
- Brain-derived exosomes are extracellular vesicles released by neurons and glial cells that enter the peripheral circulation.
- Their molecular cargo reflects the physiological and pathological state of the cells from which they originate.
- Brain-derived exosomes provide insight into neuronal function.
- Proteomic profiling of brain-derived exosomes offers a minimally invasive approach to characterize biological processes associated with cognitive outcomes following TBI.

Study objective

- Identify whether protein signatures within brain-derived exosomes distinguishes high vs. low cognitive performance in service members and veterans after TBI.
- Hypothesis
  - Brain-derived exosome protein profiles differ between cognitive performance groups.
  - Dysregulated proteins reflect pathways involved in neuroinflammation, neuronal dysfunction, and neurovascular injury.

Methods

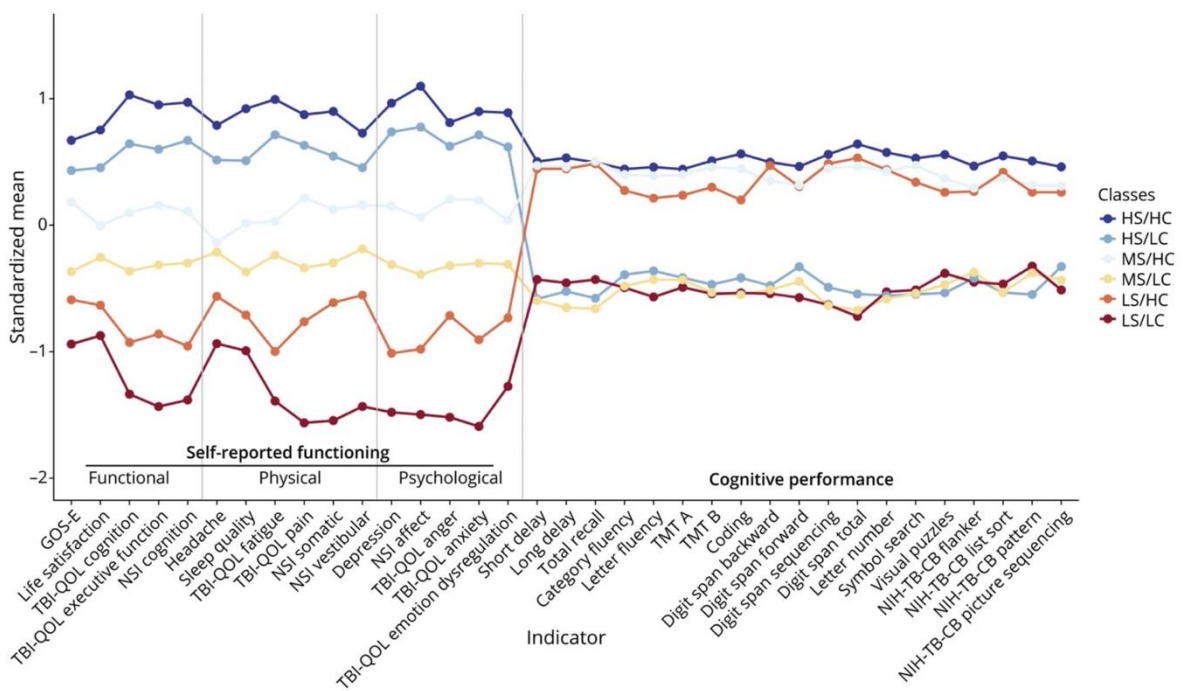
- Isolation of brain-derived exosomes
- Proteomic analysis
- Statistical analyses:
  - Differential expression
  - Logistic regression
  - ROC/AUC analyses
  - Pathway analysis



Participants

- Long-Term Impact of Military-Relevant Brain Injury Consortium–Chronic Effects of Neurotrauma Consortium (LIMBIC-CENC).
- Service Members and Veterans with a history of TBI
- Cognitive performance classified into High Cognitive (HC) and Low Cognitive (LC) groups
- N=124
- HC=66
- LC=58

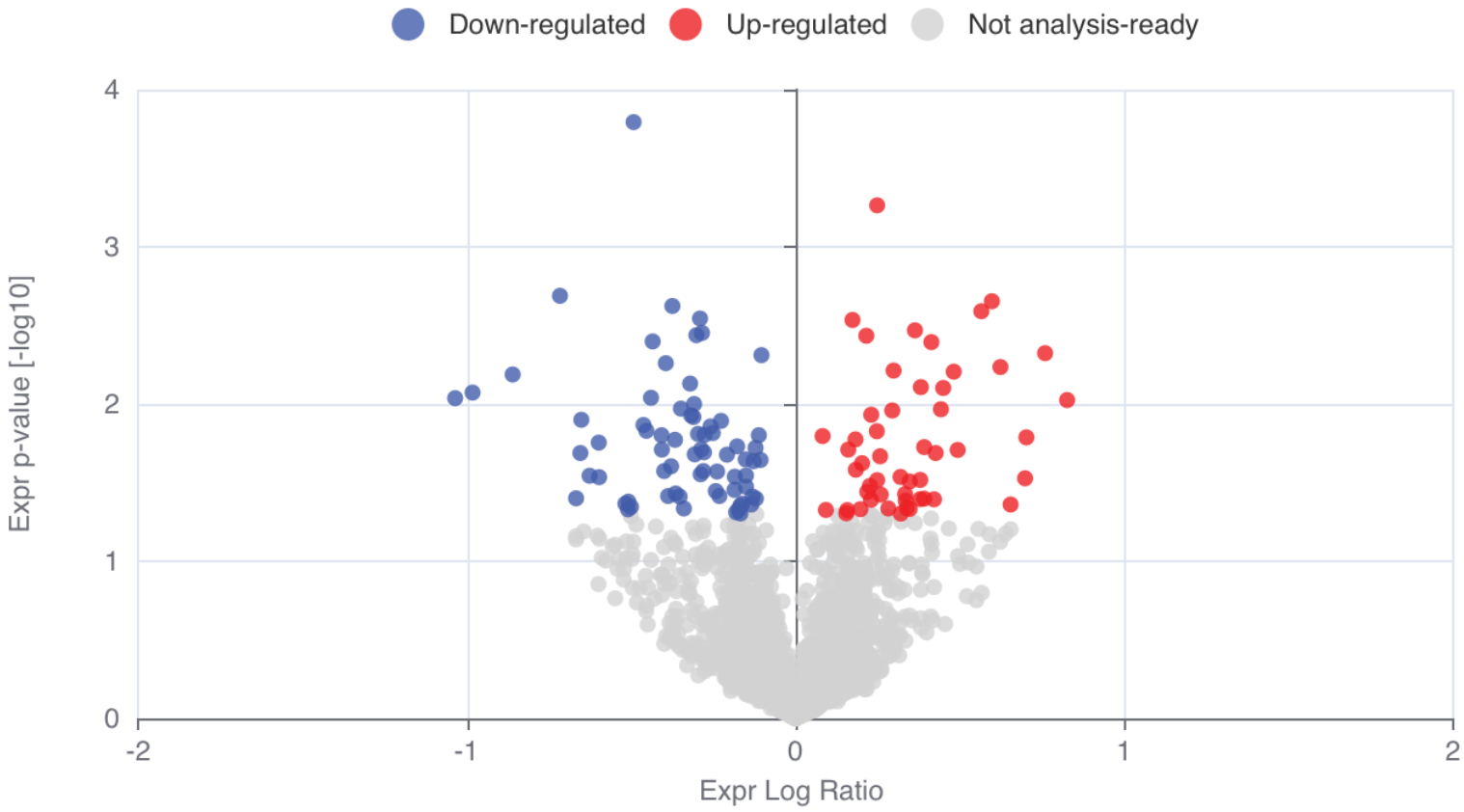
Figure 1 Six-Profile Standardized Mean Plot



(de Souza et al., 2024)

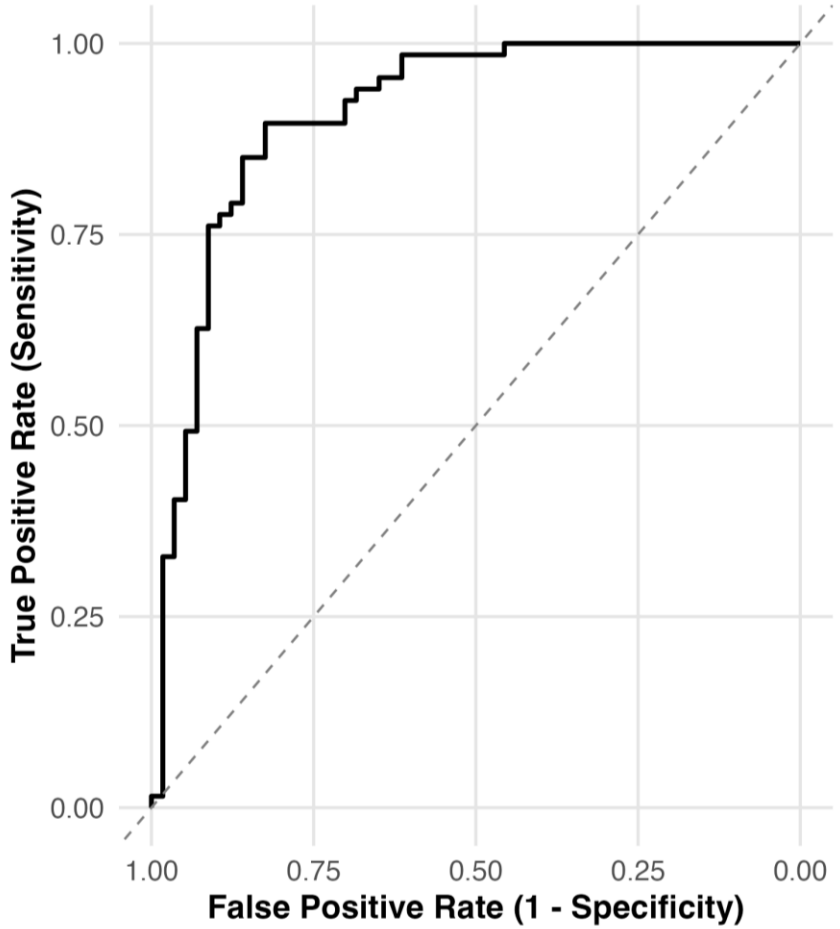
Brain-derived exosome proteins differed according to cognitive performance

- 122 differentially expressed proteins
  - 71 downregulated
  - 51 upregulated
- Significant proteins represented pathways related to:
  - Neuroinflammation
  - Synaptic function
  - Neuronal signaling
  - Neurovascular biology



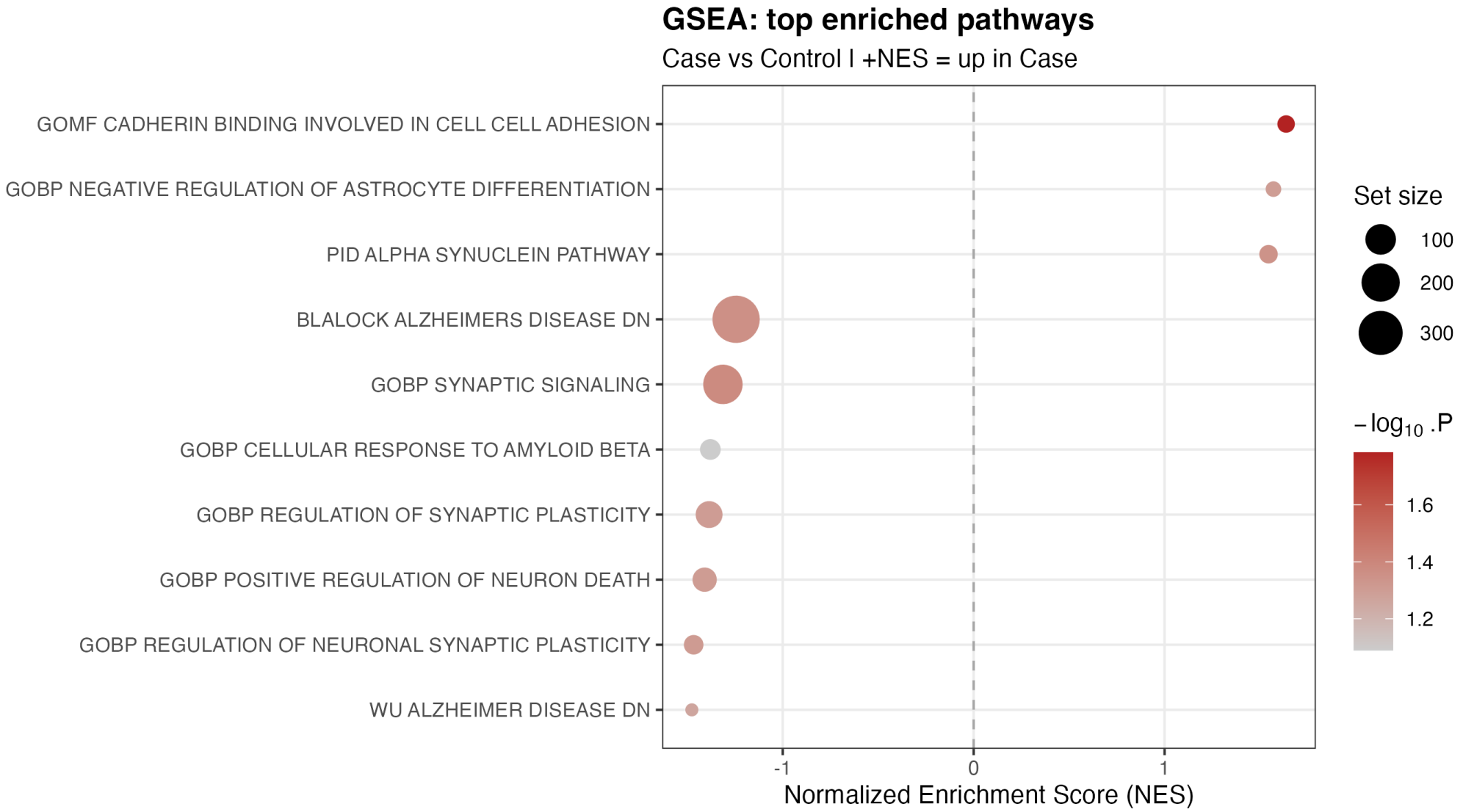
A 13-protein exosome panel distinguished HC and LC groups

Biological process	Proteins
Neuroinflammation / immune regulation	FADD, IL4R, IL10RA, RNF10
Neuronal dysfunction & intracellular trafficking	ATP6V1D, STX3, RCOR1, ERF
Neurovascular injury & tissue remodeling	ACTA2, CTSH
Oxidative stress	PON3
Protein homeostasis & cellular stress	SPAG1



Model	AUC (mean ± SD)	Sensitivity	Specificity
13-protein panel	0.899 ± 0.010	88.1%	82.5%

GSEA results



Biological interpretation

- Neuroinflammatory signaling
- Neuronal dysfunction
- Neurovascular injury
- Altered cell communication
- Biological findings are consistent with mechanisms implicated in persistent cognitive dysfunction after TBI.

Clinical implications

- Blood-based biomarkers may improve identification of individuals with lower cognitive performance.
- Exosome biomarkers may complement existing clinical assessment.
- Findings support future biomarker-driven precision medicine approaches following TBI.

Conclusions

- Brain-derived exosome proteins differed between HC and LC cognitive performance groups.
- Biomarker panels demonstrated promising discrimination of cognitive performance status.
- Findings implicate biological pathways involving neuroinflammation, neuronal dysfunction, and neurovascular injury.
- Brain-derived exosome biomarkers warrant further investigation for cognitive risk stratification after TBI.

Questions

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