



Endoplasmic Reticulum Stress Signaling Shapes Tau Pathology And Glial Reactivity After Repetitive Mild Brain Injury

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Take Home Message

Neuronal **PERK** deficiency amplifies molecular, white matter, and brain network vulnerability following repetitive mild traumatic brain injury.

INTRODUCTION

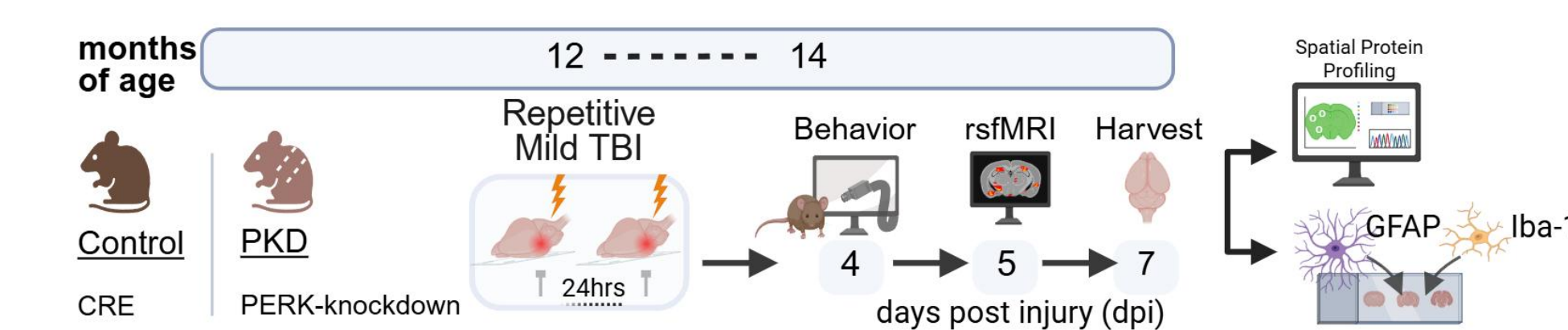
METHODS/ RESULTS

RESULTS

CONCLUSIONS

- Traumatic brain injuries (TBI) increase the risk of long-term neurodegenerative disorders, including tauopathies and Alzheimer's disease.
- Repetitive head impacts exacerbate brain injury and contribute to lifelong cognitive and emotional deficits.
- PERK (**P**rotein **K**inase **R**NA-like **E**R **K**inase) is an ER stress sensor activated after brain injury that regulates protein synthesis and adaptive cellular stress responses.

Experimental Timeline



Validation of neuronal PERK reduction

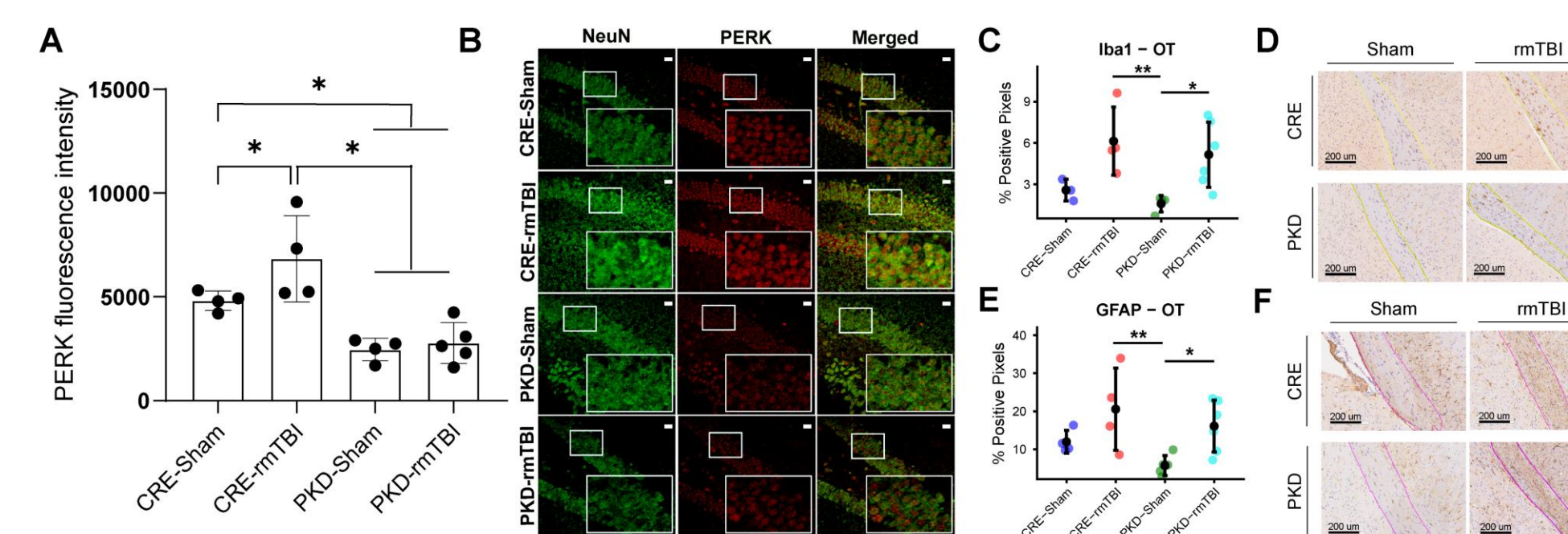


Figure 1. (A-B) Reduced PERK expression was confirmed in NeuN-positive hippocampal neurons of PKD mice. (C-F) rmTBI increased microglial (Iba-1) and astrocytic (GFAP) reactivity in the optic tract (OT). *p<0.05, **p<0.01

Low PERK signaling exacerbates white matter injury

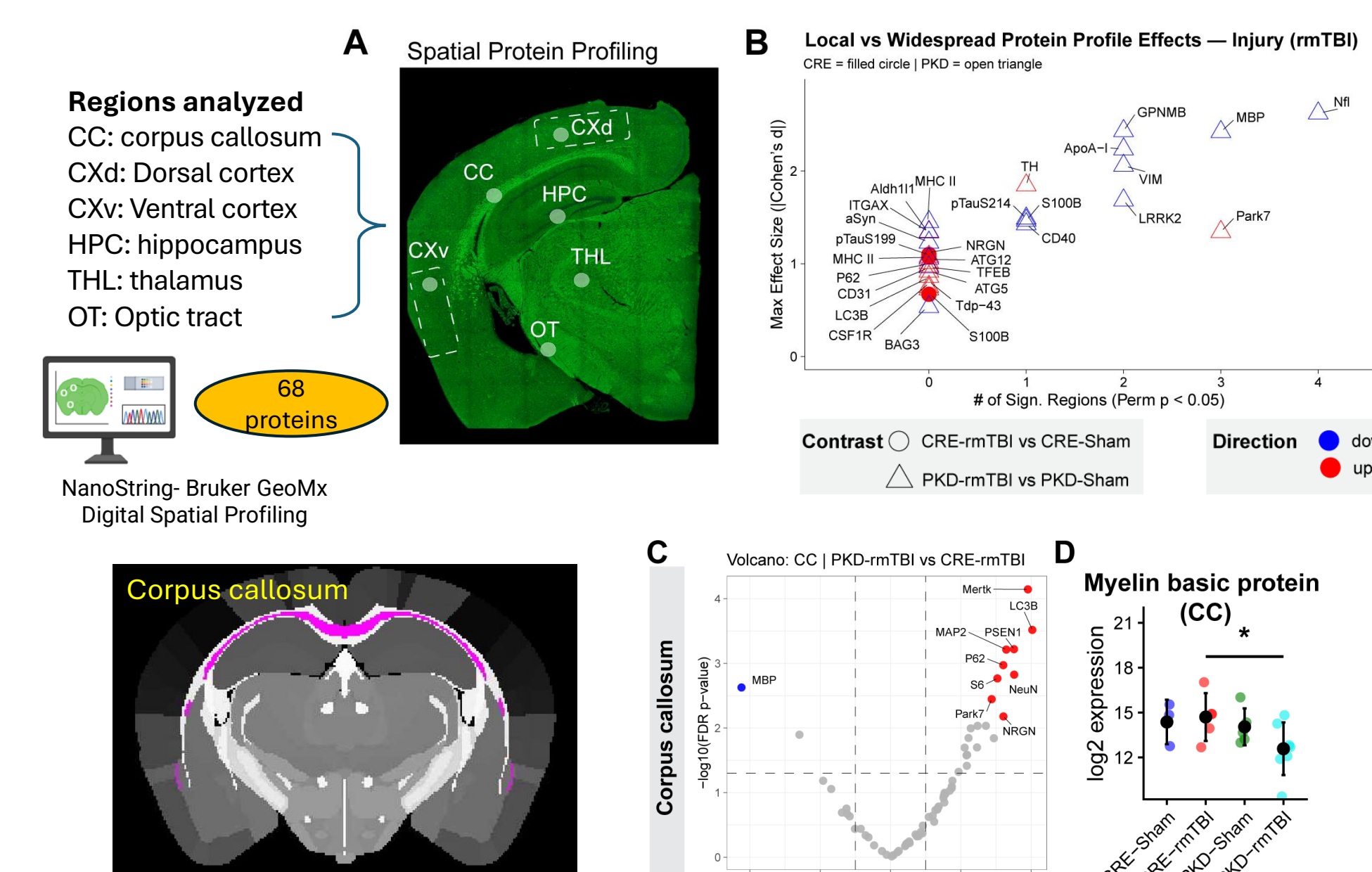


Figure 2. (A) Six brain regions were analyzed by spatial proteomics. (B) rmTBI broadly altered myelin- and axonal-associated proteins, with Myelin Basic Protein (MBP) and Neurofilament light (NfL) showing the strongest regional effects. (C-D) PERK deficiency altered corpus callosum protein profiles and reduced MBP levels following rmTBI. Scatter plots show the maximum effect size (Cohen's d) and the number of significantly altered regions. Volcano plots depict log2 fold change versus -log10(p-value); proteins with FDR < 0.05 are highlighted in red (upregulated) or blue (downregulated). *p<0.05

PERK deficiency remodels the hippocampal proteome independent of injury

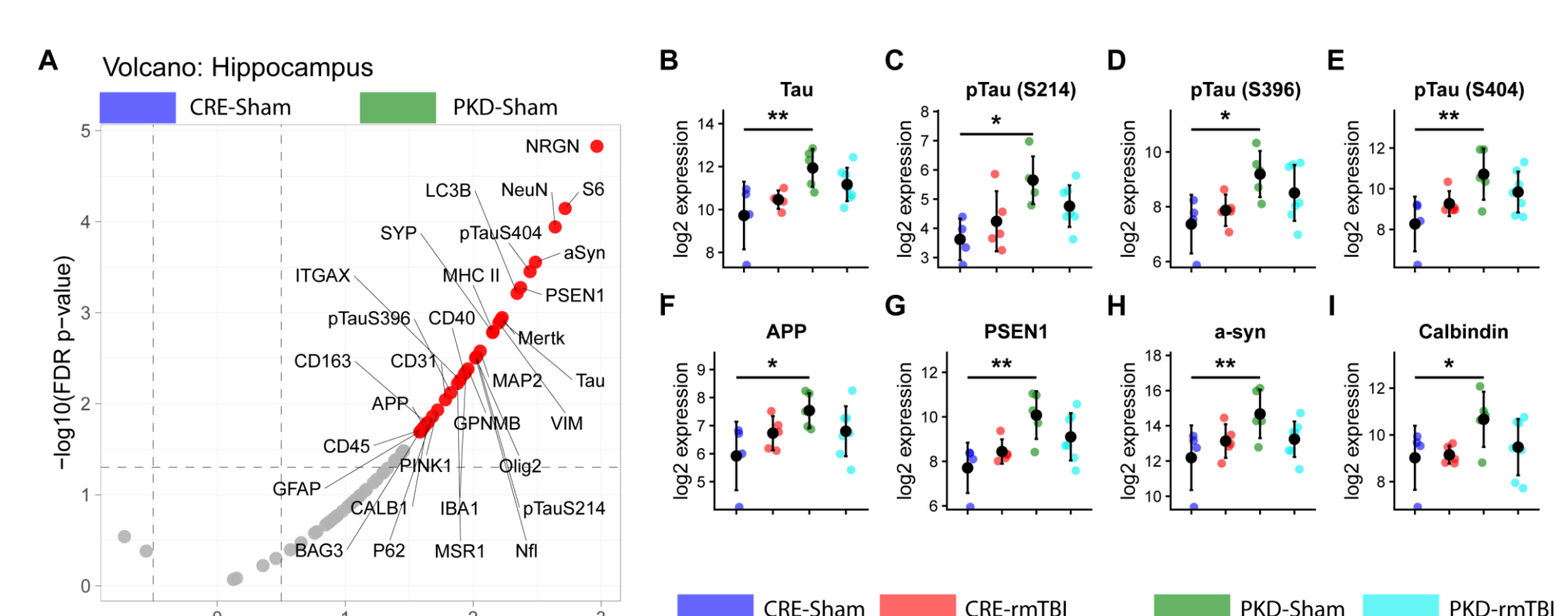


Figure 3. (A) Baseline hippocampal protein profiles differed between PKD and CRE mice, with increased expression of neuronal-, tau-, and proteostasis-associated proteins in PKD animals. (B-I) Representative proteins showed increased total Tau, phospho-Tau species, APP, PSEN1, α -synuclein, and calbindin in PKD mice. Volcano plots depict log2 fold change versus -log10(p-value); proteins with FDR < 0.05 are highlighted in red (upregulated) or blue (downregulated). These data demonstrate that PERK deficiency drives broad hippocampal molecular remodeling independent of rmTBI. *p<0.05, **p<0.01

Reduced PERK signaling weakens functional brain networks

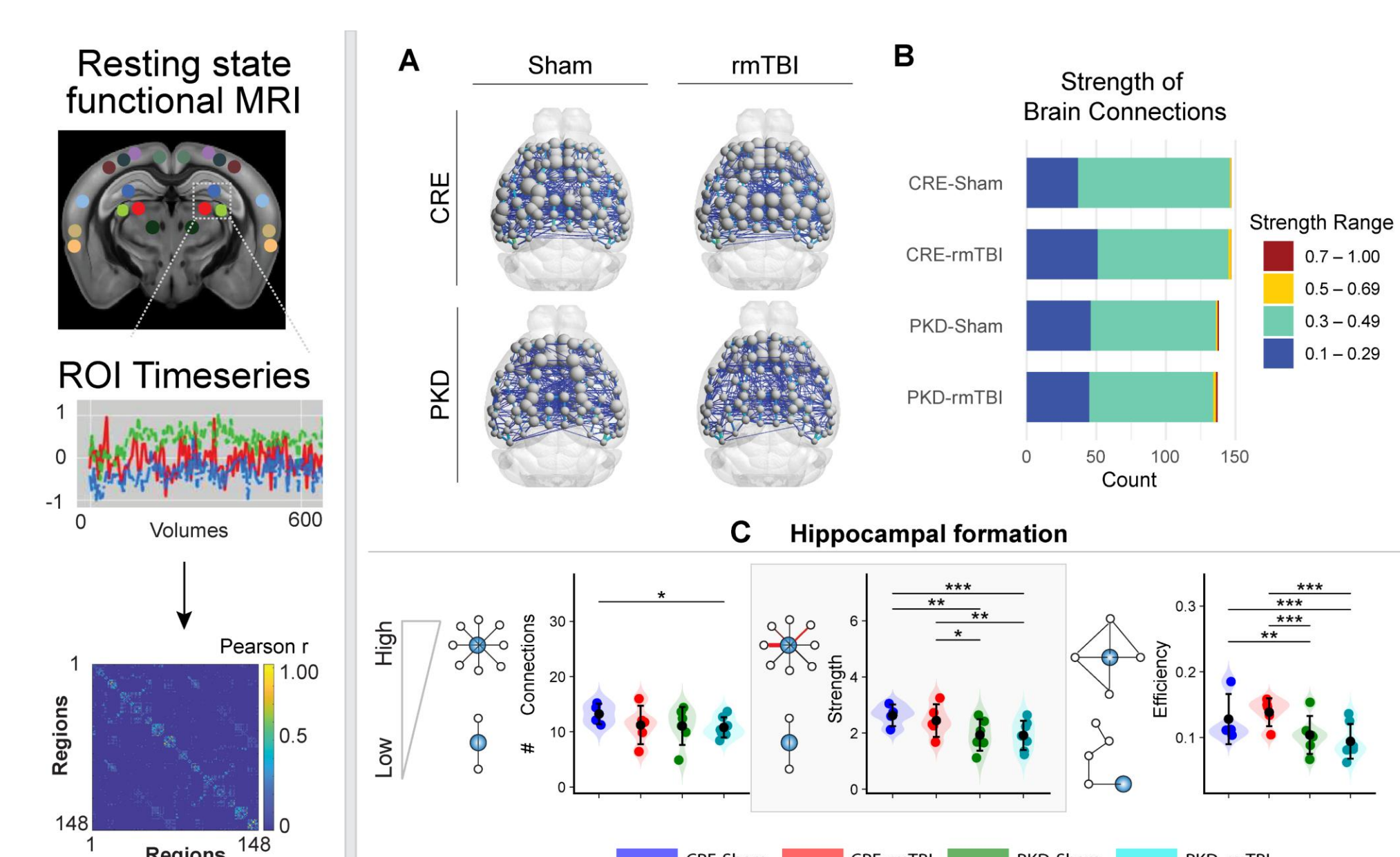
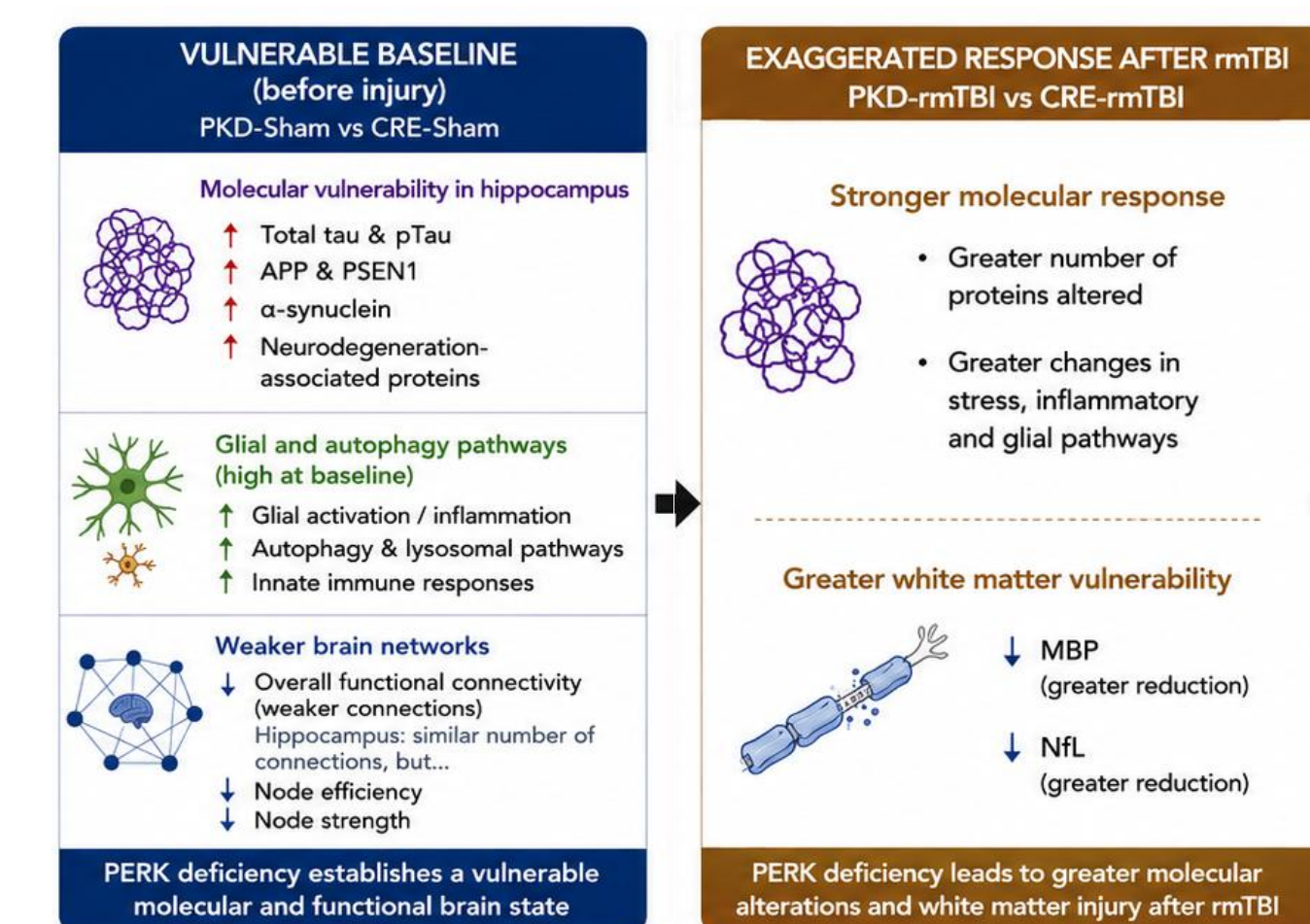


Figure 4. Resting-state fMRI was used to assess functional connectivity across 148 brain regions. (A-B) Reduced PERK signaling weakened whole-brain functional connectivity. Network strength reflects the overall connectivity of a brain region, whereas efficiency measures how effectively information is integrated across the network. (C) PKD mice exhibited impaired hippocampal network organization, including reduced connectivity strength and efficiency, compared with CRE mice. *p<0.05, **p<0.01, ***p<0.001



ACKNOWLEDGMENTS

Funding and support:

NIH/NIA grants: 1R01AG074584-01, R21AG093972, R01AG075900
NINDS grants: R01NS091329
National Science Foundation Cooperative Agreement DMR-1644779
State of Florida (USA): S10 RR025671 for MRI/S instrumentation
Department of Defense Grant: 11811993
CurePSP: 6144107400
U.S. Department of Veterans Affairs: 5I50RX003000
Alzheimer's Association grants: 2019-AARFD-644407; AARGD-21-847204, NIRG-14-322441, NIRGD-12-242642



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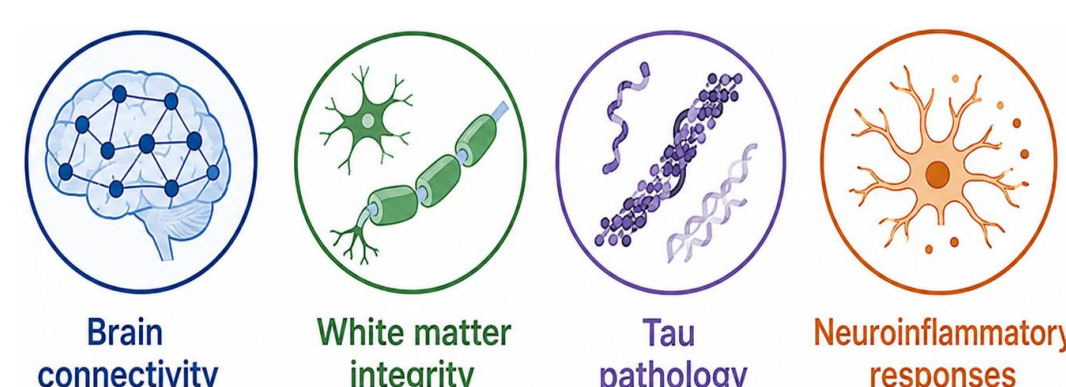
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Endoplasmic reticulum stress signaling may represent a biological determinant of vulnerability versus resilience following repetitive mild TBI (rmTBI).



TBI Model

- Closed-head injury model of engineered rotational acceleration (CHIMERA)

