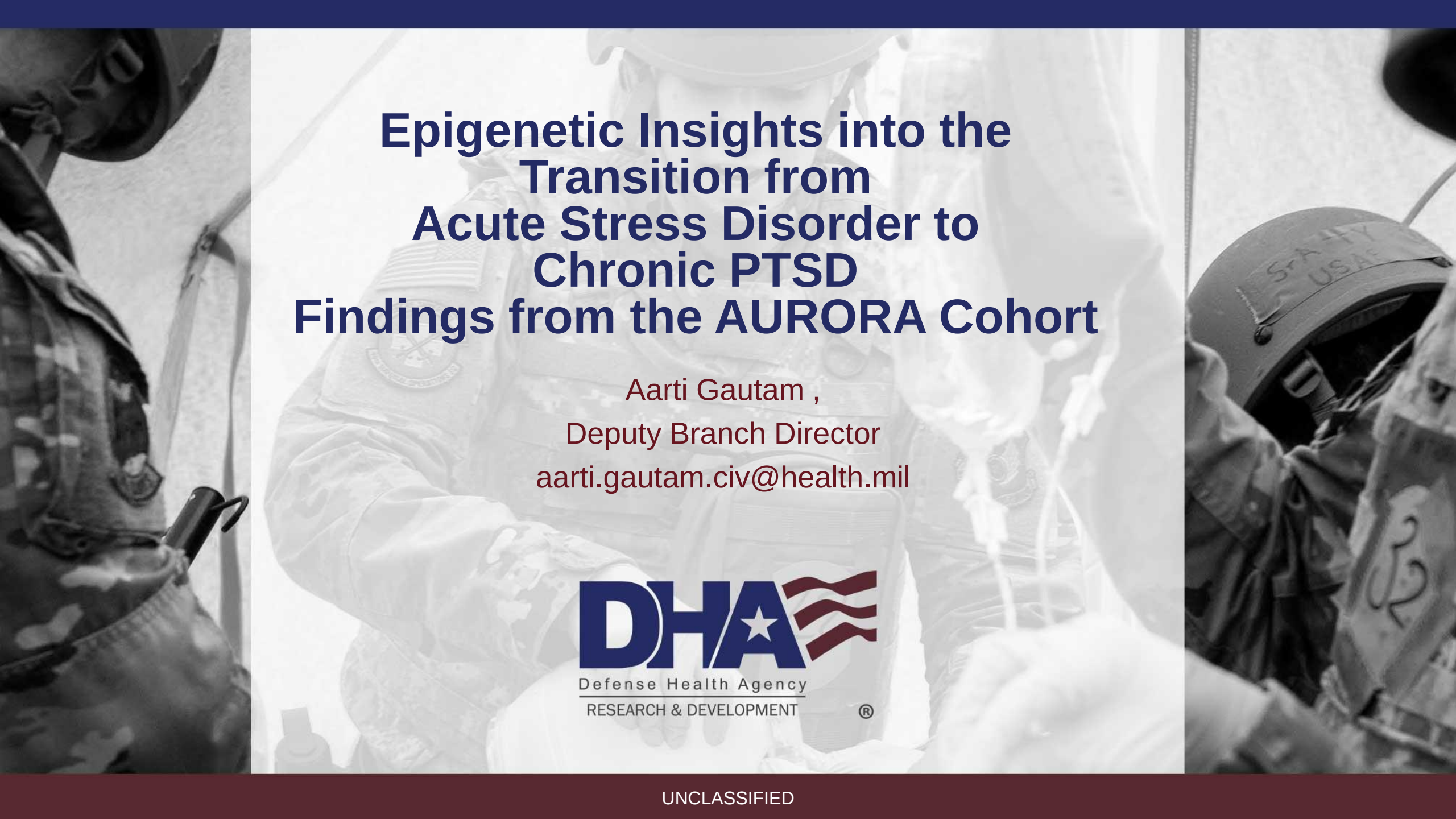




Epigenetic Insights into the Transition from Acute Stress Disorder to Chronic PTSD Findings from the AURORA Cohort

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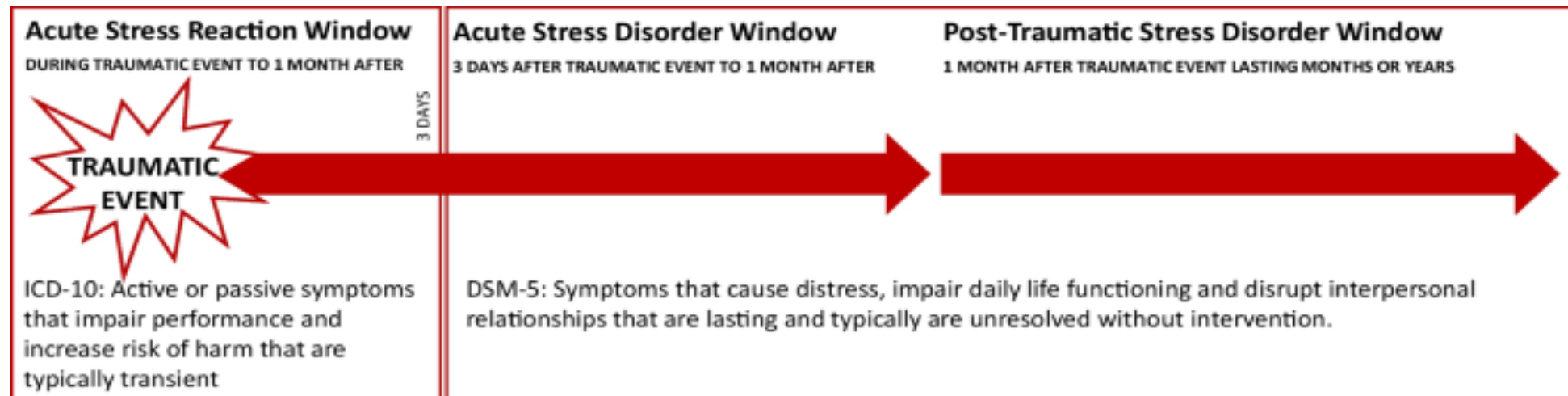
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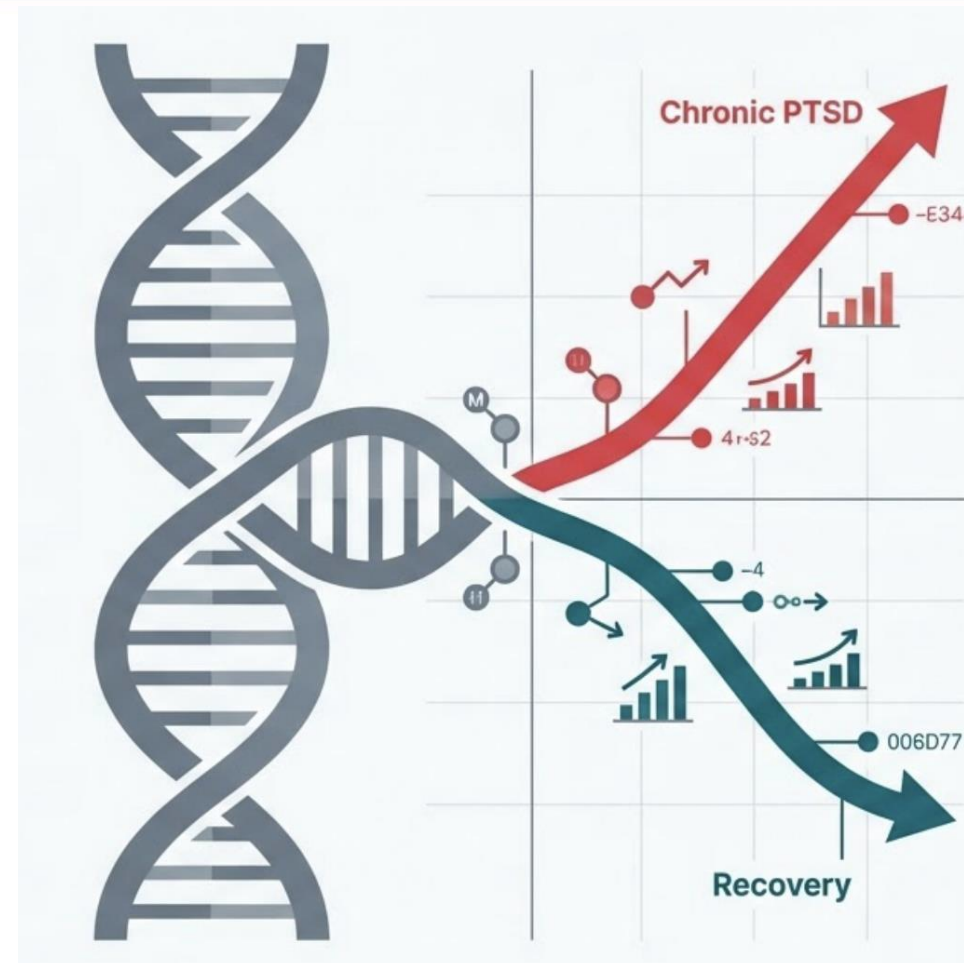
No information herein is meant to be an endorsement of any non-federal entity.

- » Trauma related disorder characterized by presence of nine or more symptoms from any of the five symptom clusters (intrusion, negative mood, dissociation, avoidance, and arousal).
- » Occurs within a month of traumatic event.
- » ASD can give rise to serious complications.
- » Current ASD diagnosis relies on patient self-reports and symptom observations.
- » Reliable biomarkers will enhance clinical practice by improving diagnostic and prognostic accuracy.



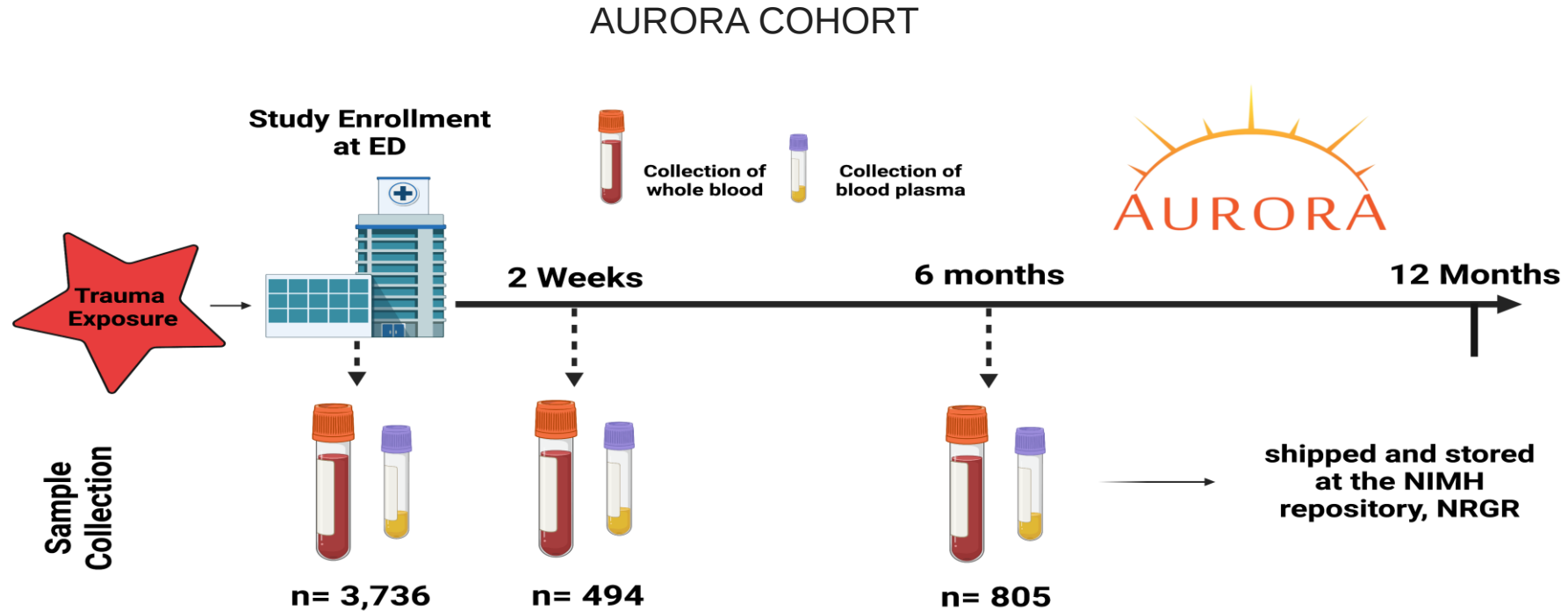
Using blood epigenetic profiles to

1. Distinguish the molecular signature of Acute Stress Disorder (ASD) from resilient outcomes
2. Further distinguish the molecular signature of “Recovery” from “Chronic PTSD”





Samuel McLean, MD, MPH

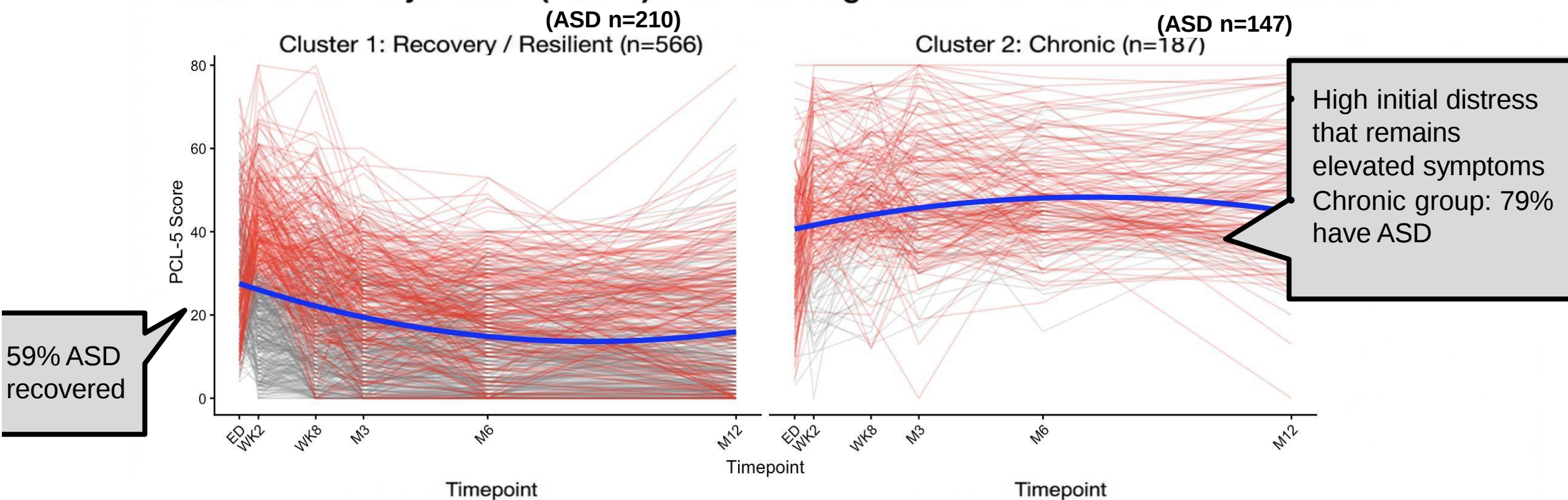


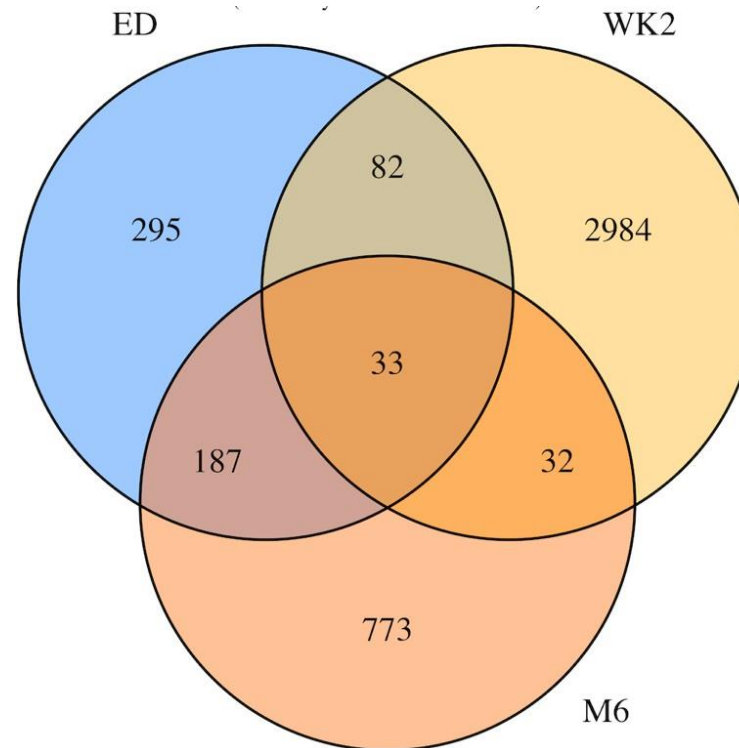
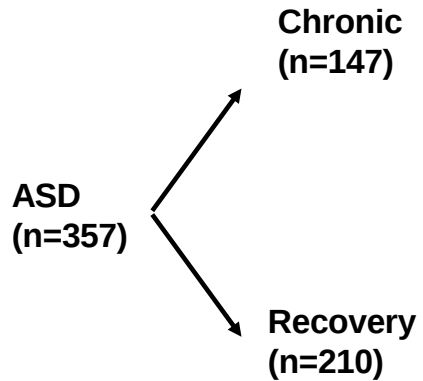
Controls vs ASD ~750 subjects were assessed at two or more time points

Cohort that tracks biobehavior data from ED admission upto a year

Clinical trajectories reveal two distinct populations: Resilient Recovery versus Chronic Symptomology

Latent Class Trajectories (LCMM) based on longitudinal PCL-5 Scores over 12 months

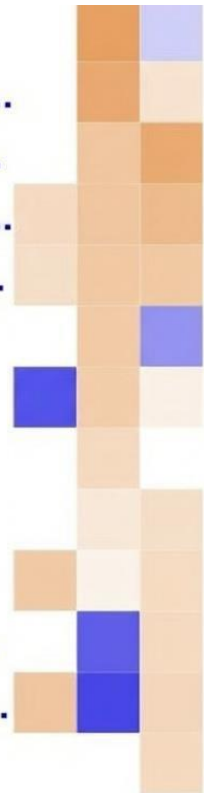




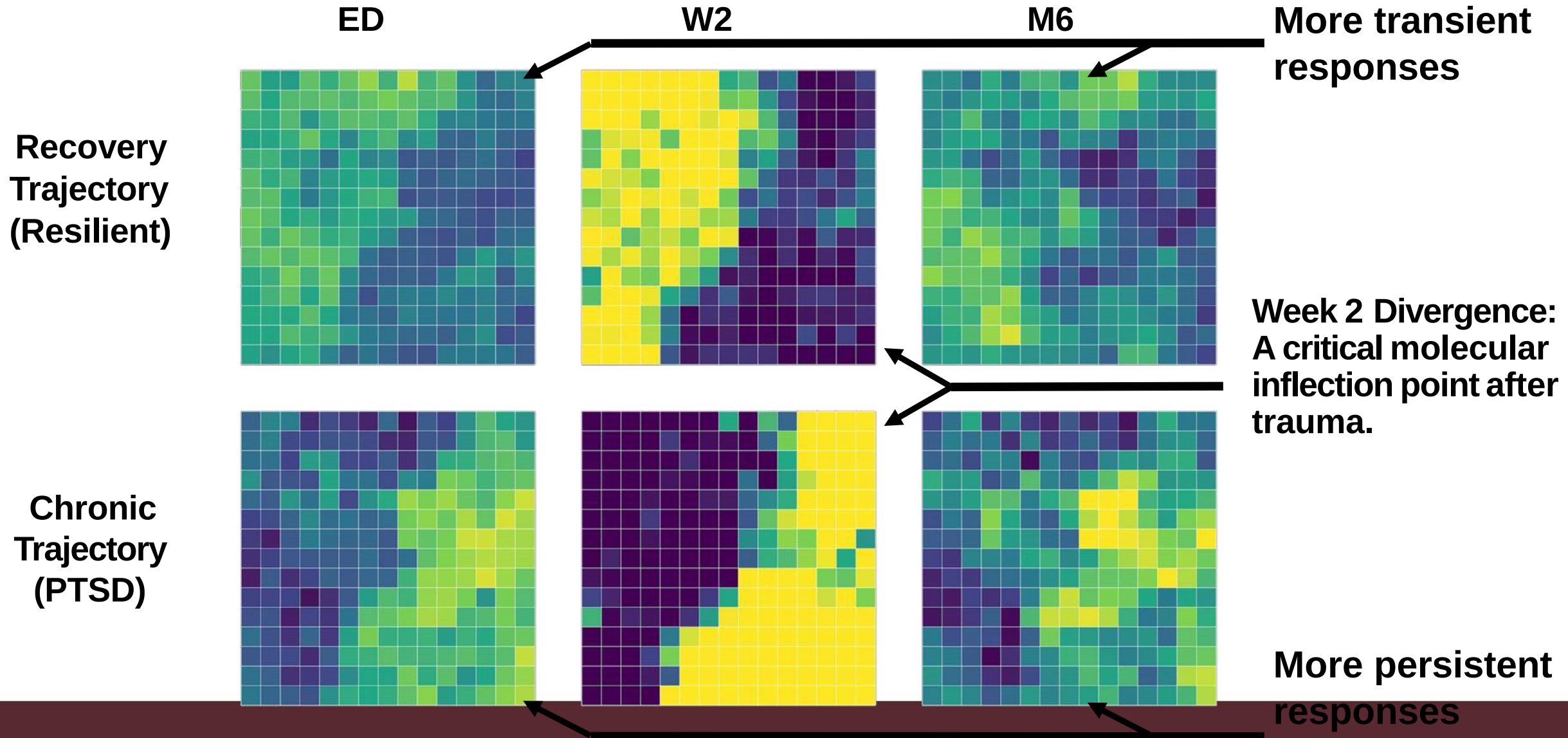
Activation Z-score
-3.000 3.500

ED W2 M6

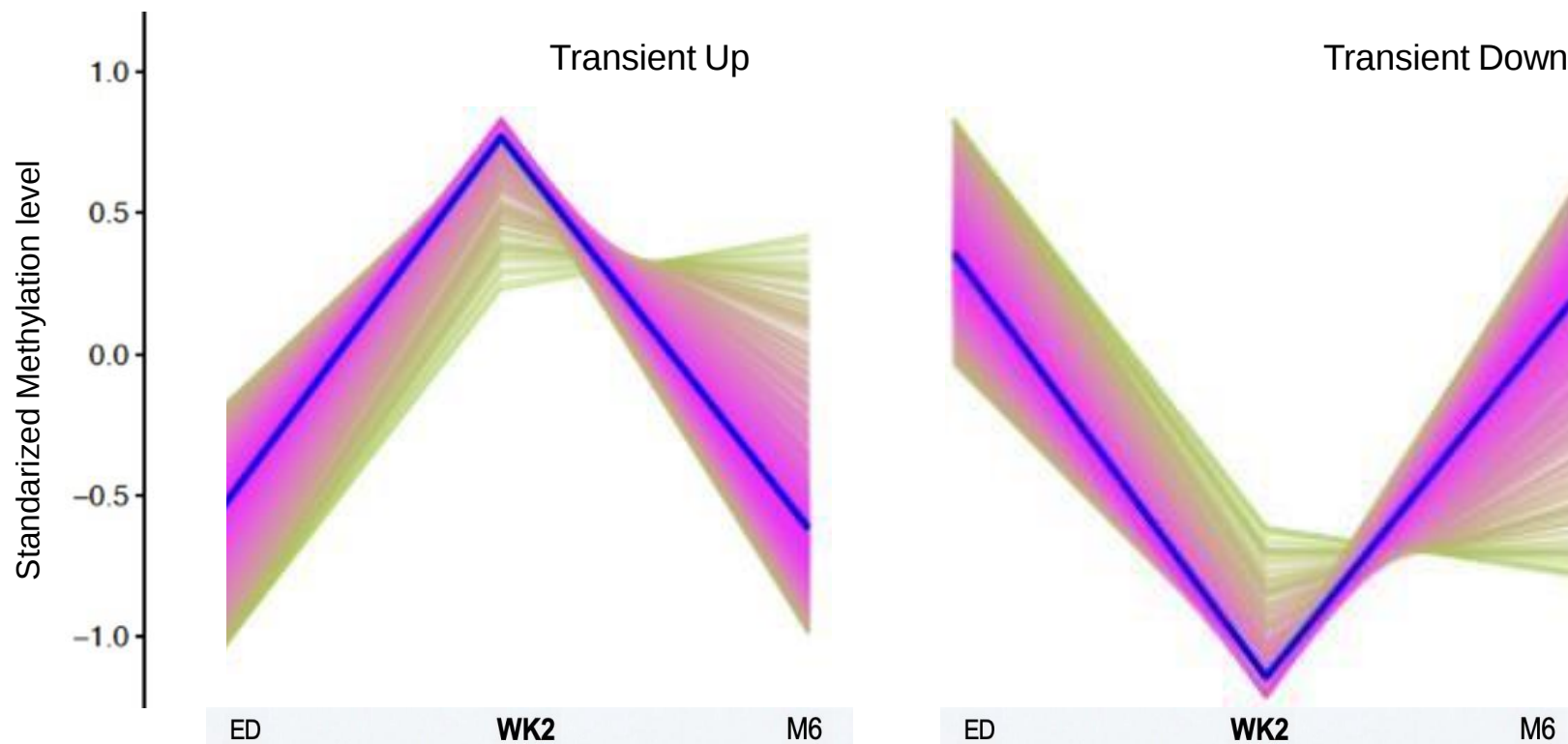
Netrin Signaling
Role of NFAT in Cardiac Hyp...
Dopamine-DARPP32 Feedb...
Pancreatic Secretion Signalin...
Glutaminergic Receptor Sign...
Calcium Signaling
Motor/cytoskeleton signaling
nNOS Signaling in Neurons
G Beta Gamma Signaling
CREB Signaling in Neurons
GABAergic Receptor Signali...
G-Protein Coupled Receptor...
Oxytocin Signaling Pathway



Methylation Profiles in Recovery and Chronic Groups Are Fundamentally Distinct



The Adaptive Pulse

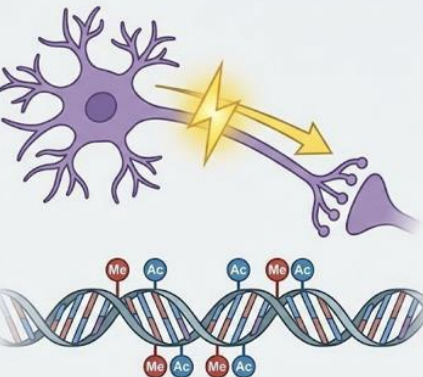


Recovery Group has significantly MORE transient response genes:

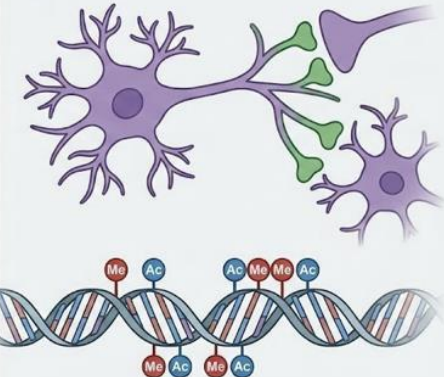
Transient Up: n=1567 (Recovery) vs n=724 (Chronic)
Transient Down: n=1344 (Recovery) vs n=751 (Chronic)

Shared Epigenetic Responses in Neuronal Excitability and Plasticity

Neuronal Excitability

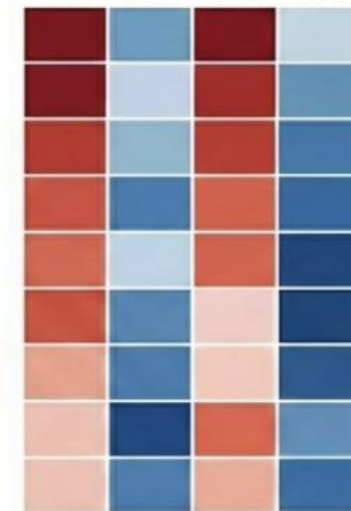


Neuronal Plasticity



Calcium Signaling
White Adipose Browning
Nitric Oxide Signaling
Opioid Signaling
Motor/cytoskeletal signaling
Glutamatergic Signaling
Pancreatic Secretion
Netrin Signaling
CREB Signaling

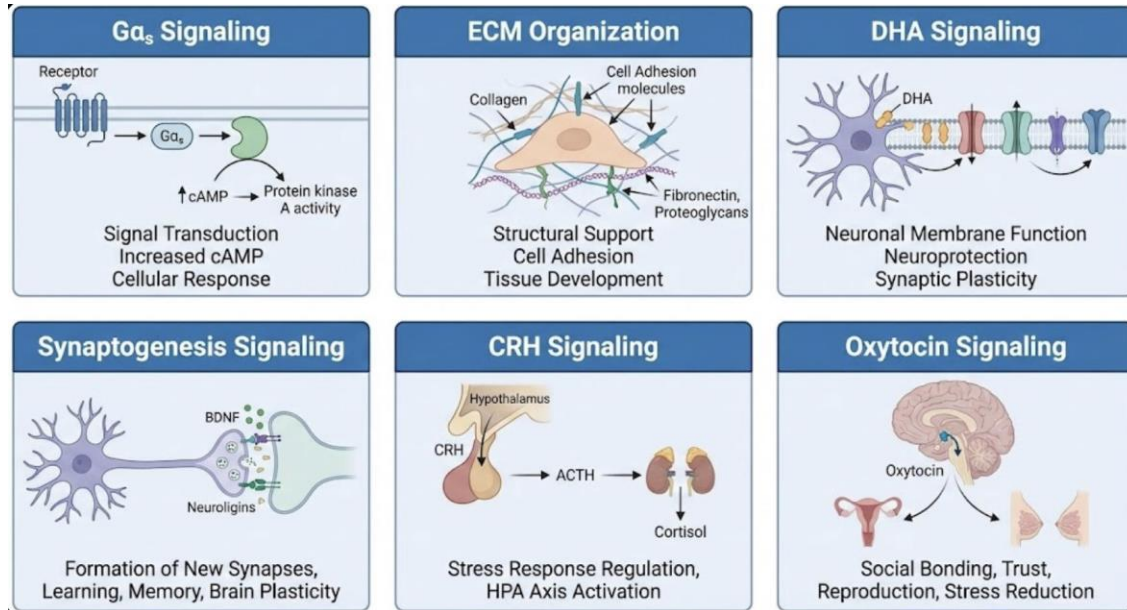
Chronic Recovery
TU TD TU TD



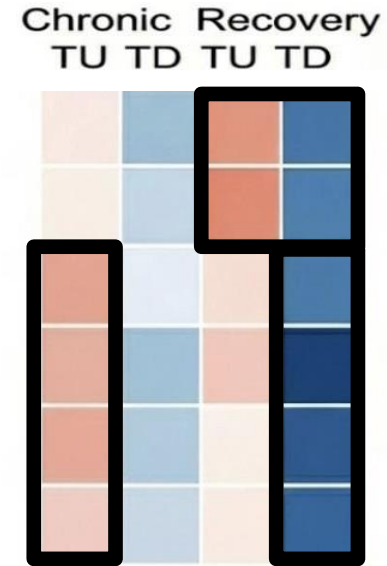
Darker color means more significance

Tissue Organization in “Transient” Responses

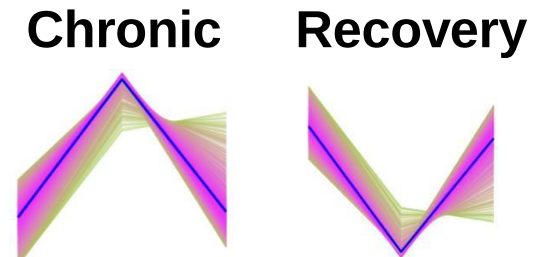
Distinct Pathways



Gα_s signaling
ECM Organization
DHA Signaling
Synaptogenesis Signaling
CRH Signaling
Oxytocin Signaling



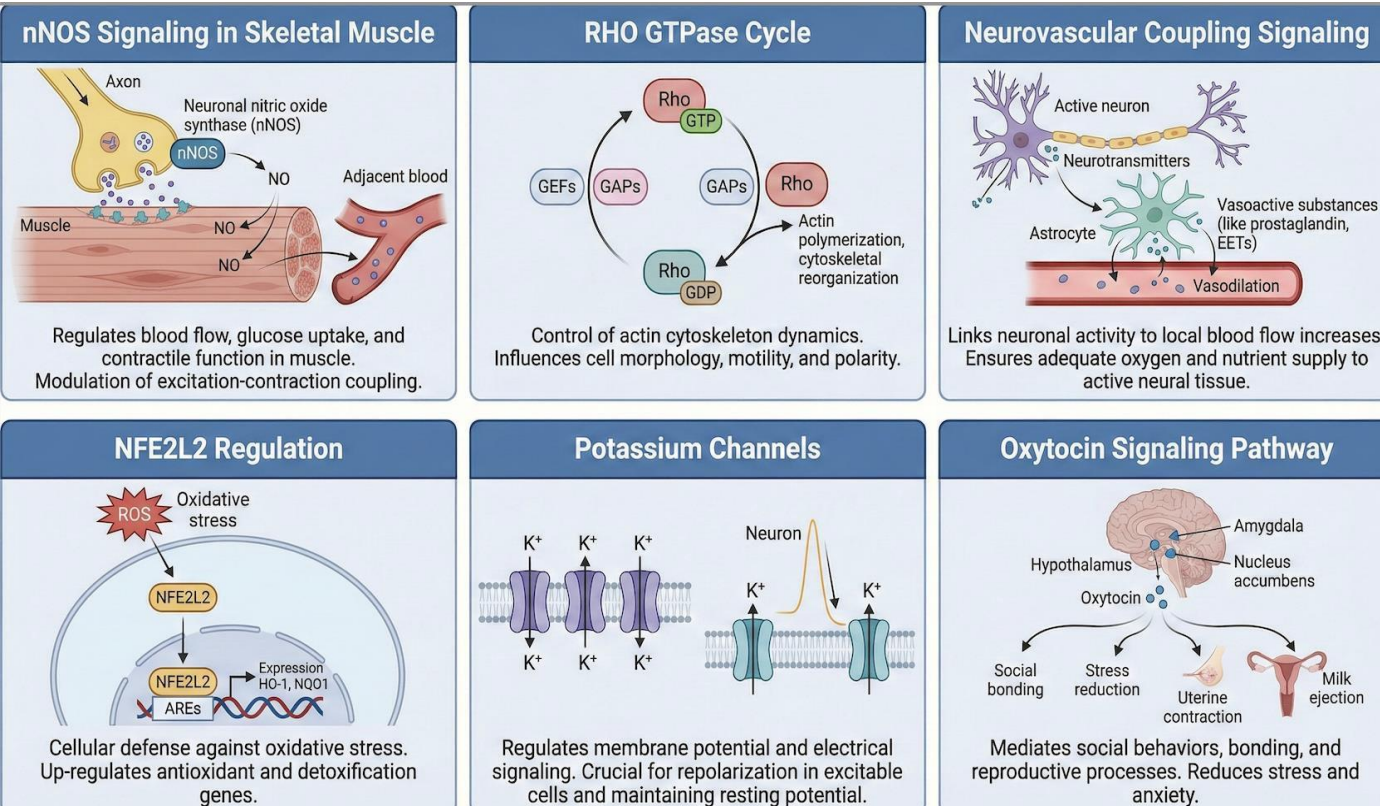
Oxytocin Signaling





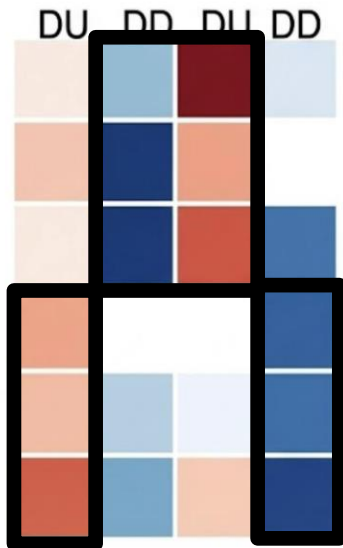
Chronic patients have twice more genes in delayed response than Recovery group

Insight: The inability to return to baseline molecular expression is a hallmark of chronic pathology. The biological machinery gets 'stuck' or reacts too late.



nNOS Signaling
RHO GTPase
Neurovascular Coupling
NFE2L2 Regulation
Potassium Channels
Oxytocin Signaling

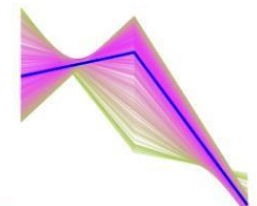
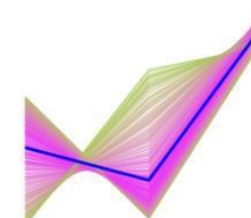
Chronic Recovery



Chronic

Recovery

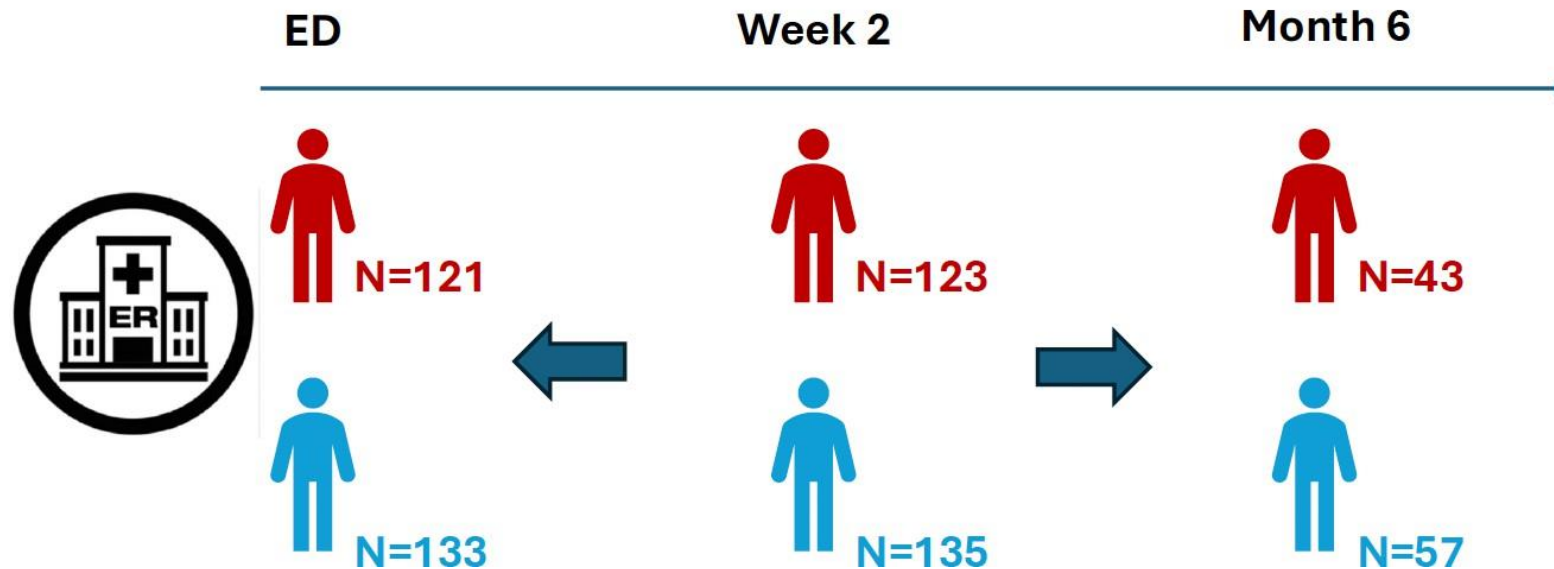
Oxytocin Signaling



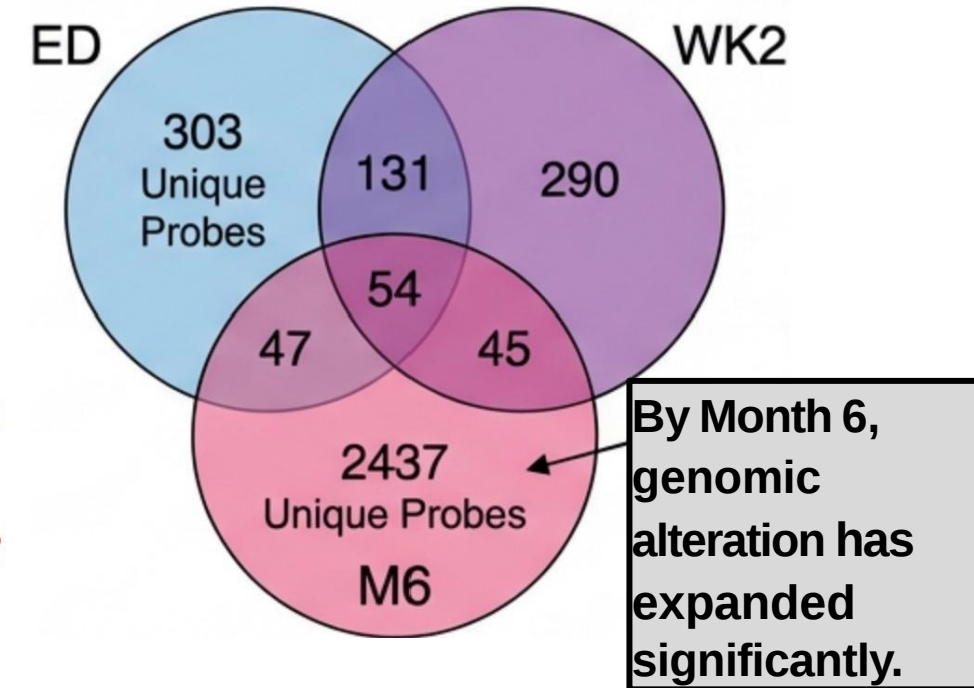
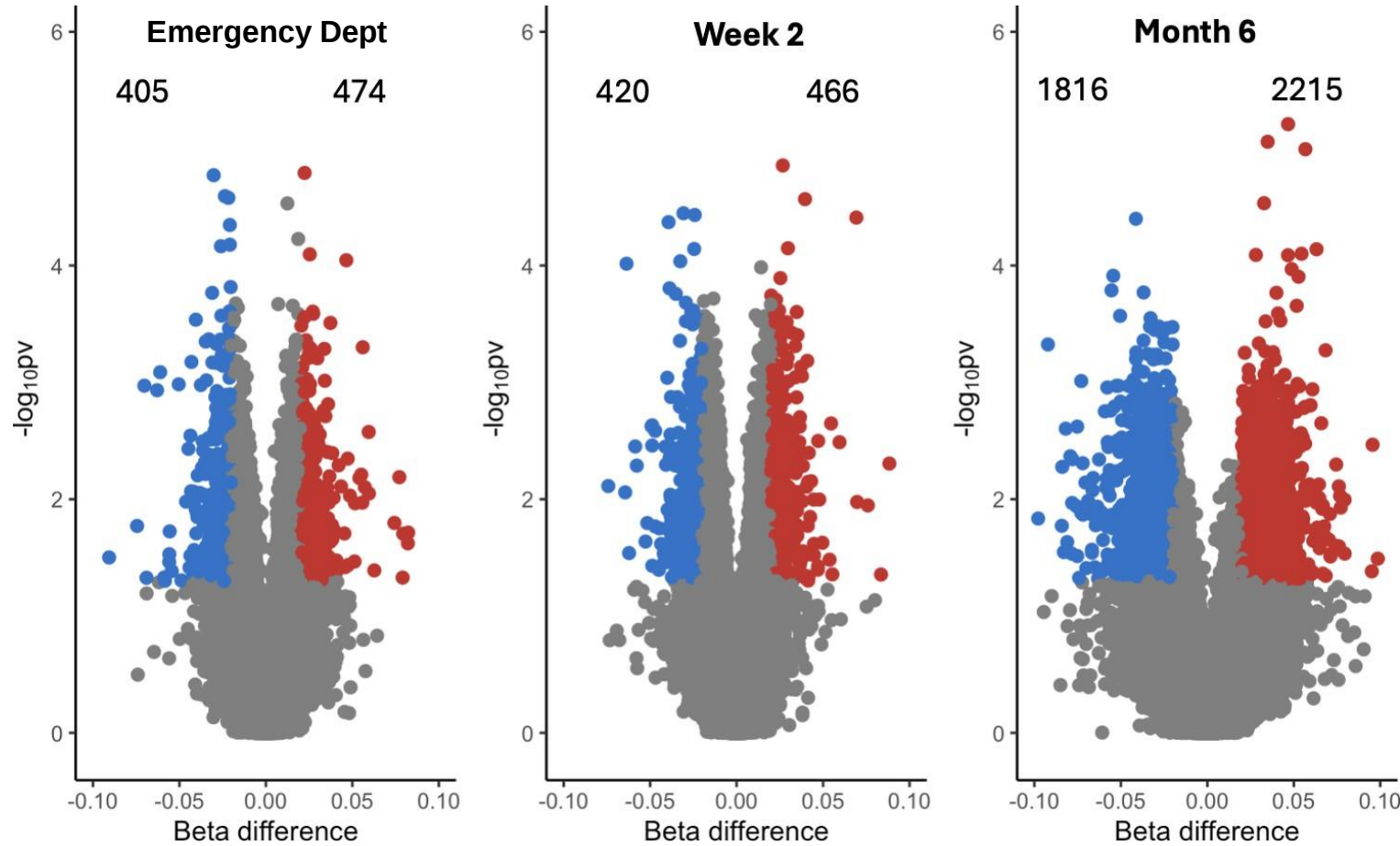
Tracking Longitudinal DNA Methylation Profiles of ASD vs. Control Groups Across Three Critical Timepoints

Red = Participants with ASD

Blue = Control Participants



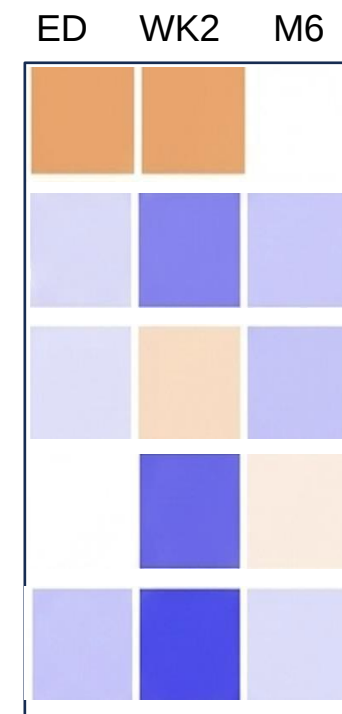
Trauma Induces Widespread Methylation Changes Across the Genome



The Epigenetic Response Focuses on Neuro-Regulatory and Cardiac Pathways

**Top Enriched Pathways in
ASD vs Control**

Opioid Signaling Pathway
Cardiac Hypertrophy Signaling
CREB signaling in Neurons
Glutamatergic Receptor Signaling
Serotonin Receptor Signaling

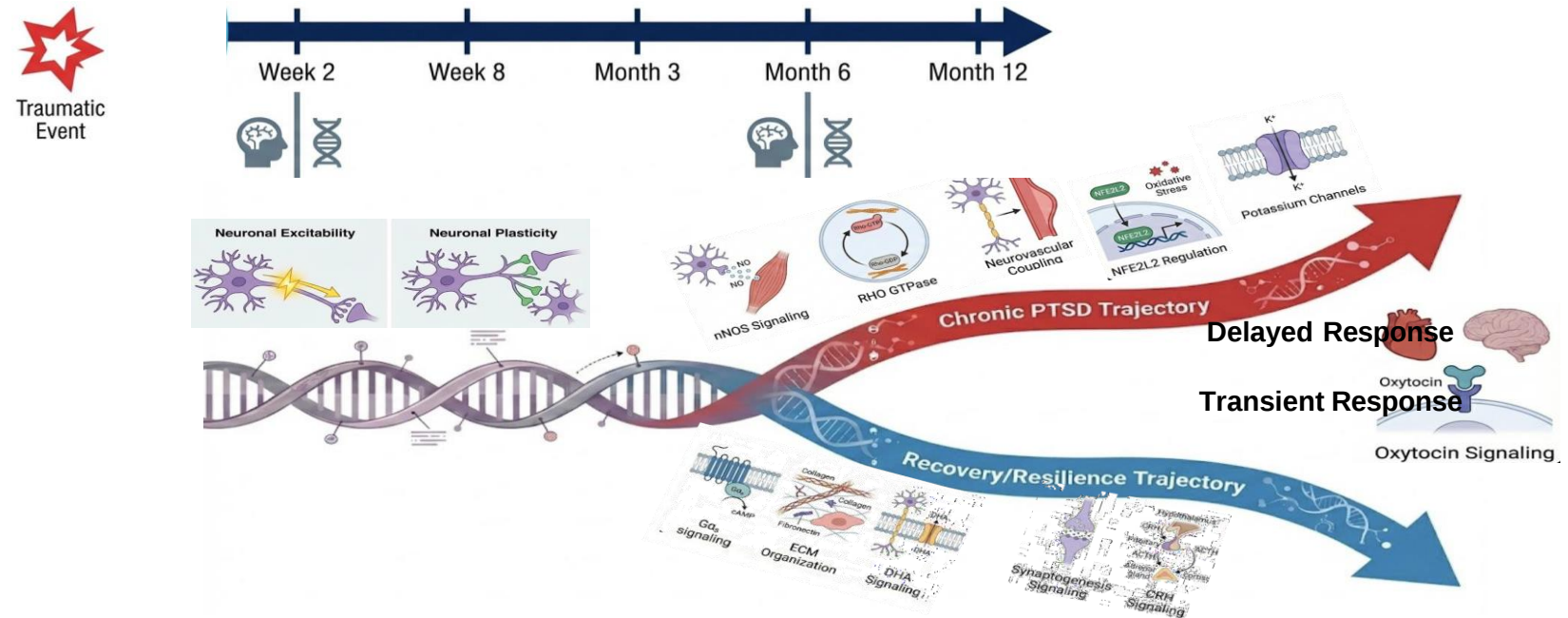


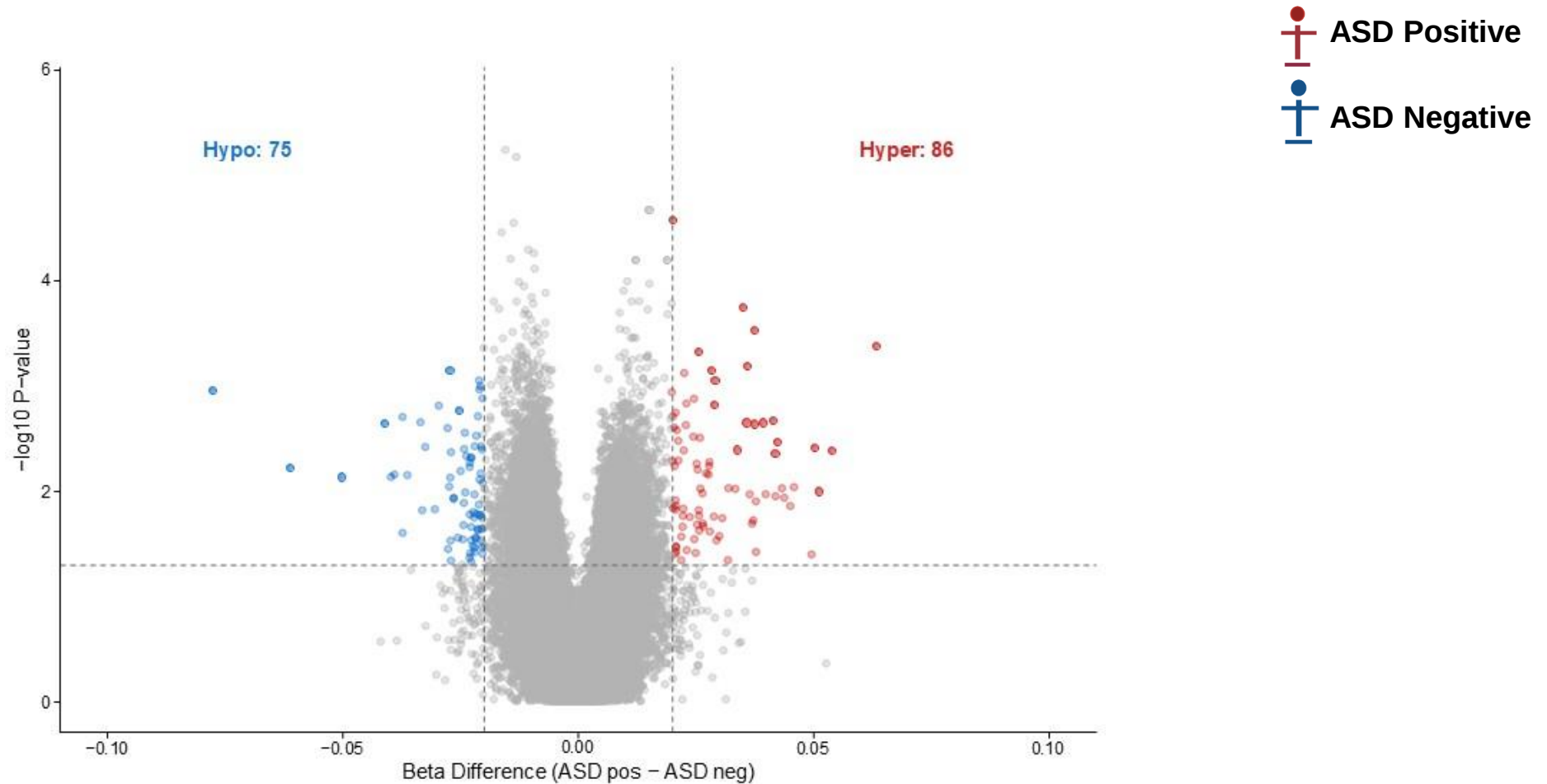
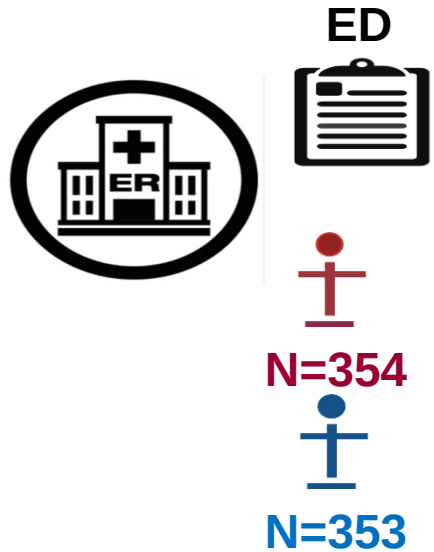
- » DNA methylation profiles associated with onset of ASD at early timepoints.
- » We utilized longitudinal DNA methylation profiling to characterize the evolving methylome.
- » We Identified specific regulatory trajectories that distinguish successful homeostatic recovery from the entrenched epigenetic remodeling associated with symptom chronicity.
- » Cross-cohort analysis identified common methylation sites in civilian and military relevant cohort
- » These methylation sites are enriched in biological pathways related to neuronal functions.
- » Future
 - » Validation

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- NYU Langone Health
Dr. Charles Marmar and his team
- Harvard Uni/McLean Hospital
Dr. Kerry Ressler
- NIMH team





AURORA overcomes diagnostic fragmentation by tracking biobehavioral data from the emergency room through one year of recovery.

