Identification of DNA Methylation Signatures of Acute Stress Disorder

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Abstract

Background- A significantly large body of military personnel that experience traumatic events develop acute stress disorder (ASD), leading to performance deficiency and dampen the team's morale. ASD manifests between two days and four weeks after trauma exposure, distinguishing it from Post-Traumatic Stress Disorder (PTSD), which typically develops after a month. There is growing evidence that epigenetic processes such as DNA methylation (DNAm) play an important role in the etiology of psychological disorders. This study aims to examine the longitudinal changes in the DNAm profile of individuals with ASD admitted to Emergency department post trauma.

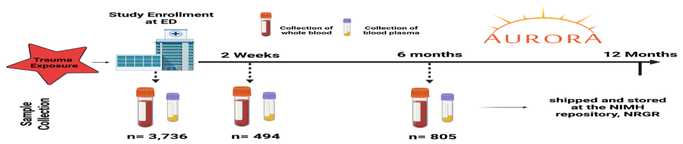
Methods- Selected participants from Advancing Understanding of RecOvery afteR traumA (AURORA) cohort were included. Each participant received a baseline Emergency Department (ED) assessment along with follow-up self-report surveys 2 weeks and 6 months later. Blood samples were collected followed DNAm assays using EPIC BeadChip.Cross-sectional and longitudinal analyses of methylation data, adjusting for covariates such as age, gender, education, and cell composition was completed. The differentially methylated genes were submitted to Ingenuity Pathway Analysis for pathway enrichment.

Results- The cohort consisted an average age of 40 with 270 male and 491 female participants. This sub-set was mainly non-Hispanic (89%) and 10% Hispanic with 23% college degree, 66% high school and above and 11% below high school level. We analyzed 1556 samples, including 731 samples at ED, 269 samples at wk2, and 556 samples after 6 months. Differential and temporal analysis identified significant probes at each time point. Pathway analysis showed significant dysregulation in well-known neurocircuit signaling pathways, insulin signaling, and cardiovascular pathways when comparing ASD and control groups. Furthermore, when tracing the week 2 subjects back to the early developmental stage at ED, we identified the onset of dysfunction in certain neurocircuit signaling pathways.

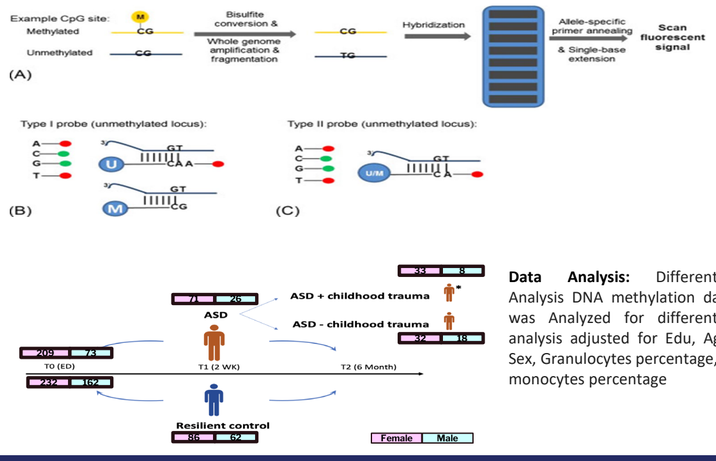
Conclusions- Our findings provide important insights into the epigenetic changes during the developmen
of ASD etiology. These data is consistent with known changes in neural circuits and pathways related to th
common comorbidities of diabetes and heart diseases. These results may inform the development of nev
screening methods to identify ASD, and those in risk of developing PTSD, enabling early intervention t
mitigate further negative impacts.

Methods

Cohort Description: Advancing Understanding of RecOvery afteR traumA (AURORA)

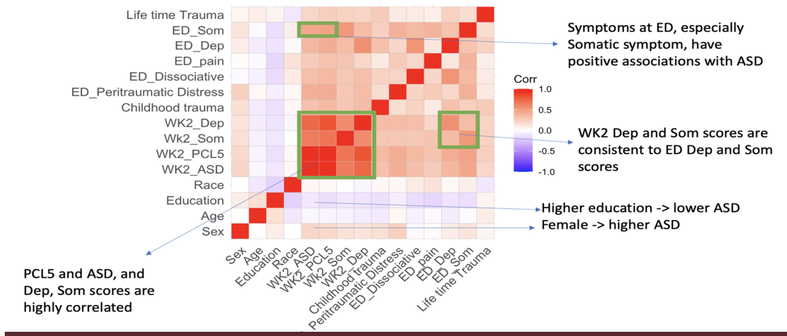


Assay: DNA methylation assay

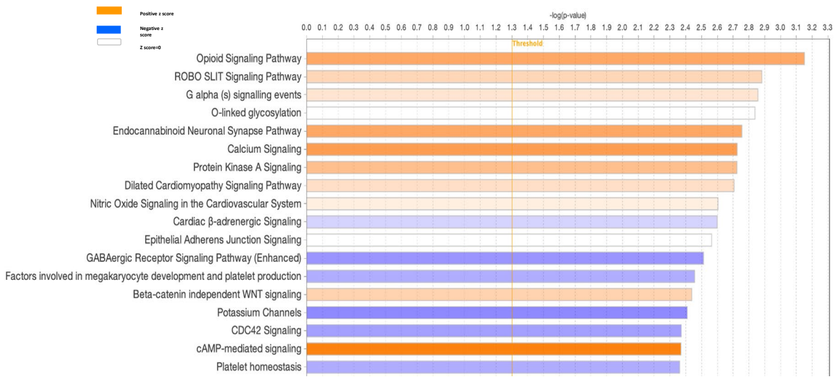


Data Analysis: Differential Analysis DNA methylation data was Analyzed for differential analysis adjusted for Edu, Age, Sex, Granulocytes percentage, monocytes percentage

Association of Clinical Variables



Significantly enriched pathways at ED visit



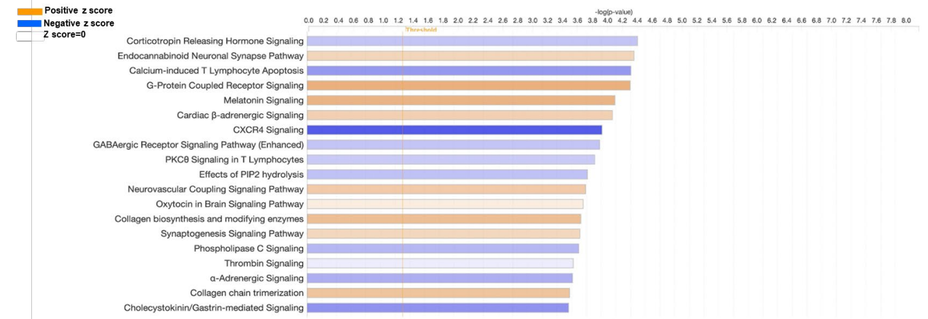
Significantly enriched pathways at 2weeks

Serotonin receptor signaling
Dopamine signaling,
CREB signaling
Glutaminergic receptor signaling
Opioid signaling
Neuropathic pain signaling

Pancreatic secretion signaling
Insulin secretion signaling

Nitric Oxide signaling in the cardiovascular system
NFAT in cardiac hypertrophy

Significantly enriched pathways at 2weeks(contd)



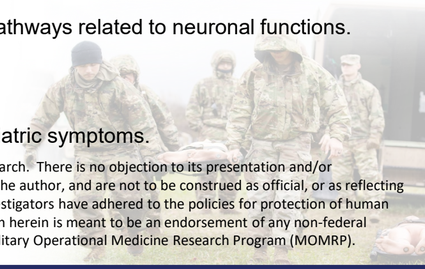
Corticotropin releasing hormone signaling
GABAergic Receptor Signaling
CXCR4 signaling -- promote wound repair and regeneration

List of Top 10 common genes

- KCNMA1: synaptic regulator of neuronal excitability
- TRAPPC9: associated with major depressive disorder
- DLGAP2: associated with major depressive disorder and PTSD
- STK32B : Increased Risk of Anxiety Disorder
- WWOX: associated with PTSD and MDD
- MRPS28:mitochondrial ribosomal protein and role in Psychiatry diseases
- LINC00616: long non-coding RNA involved in Ferroptosis, regulated cell death process
- PPFIA4: found to distinguish antidepressant responders
- OPCML: Opioid Binding Protein/cell Adhesion Molecule role in MDD
- COL25A1:Collagen alpha protein in Alzheimer Disease

Future Directions

- We identified DNA methylation profiles in blood samples that are associated with onset of ASD at early timepoints.
- These methylation sites are enriched in biological pathways related to neuronal functions.
- Ongoing and next steps
  - Validation on a new external cohort.
  - Association with severity of ASD.
  - Relationship with long term assessment of psychiatric symptoms.



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