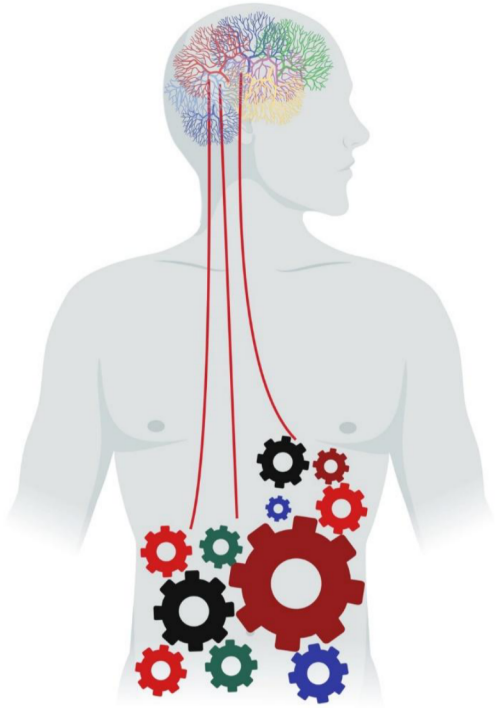
Insulin Resistance: A biomarker of Allostatic load: Implications for Premature Cognitive Aging



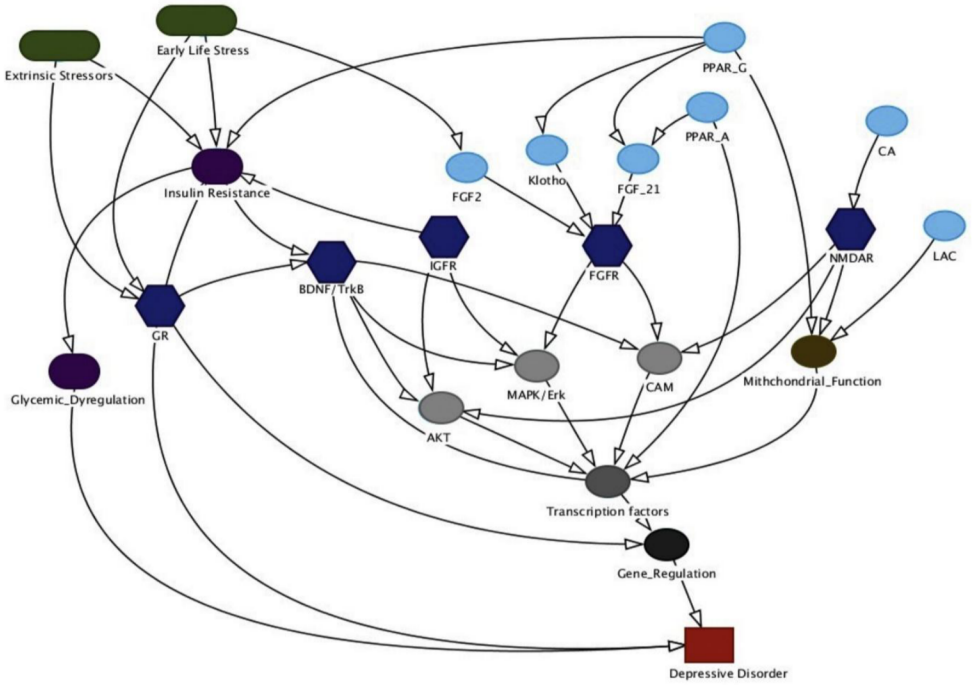
Alison Myoraku, M.S.

Research Data Analyst
Center for Neuroscience in Women's Health
Department of Psychiatry and Behavioral Sciences
Stanford University School of Medicine

Stanford Mood Disorders Day
8.20.22

What is Allostatic Load?

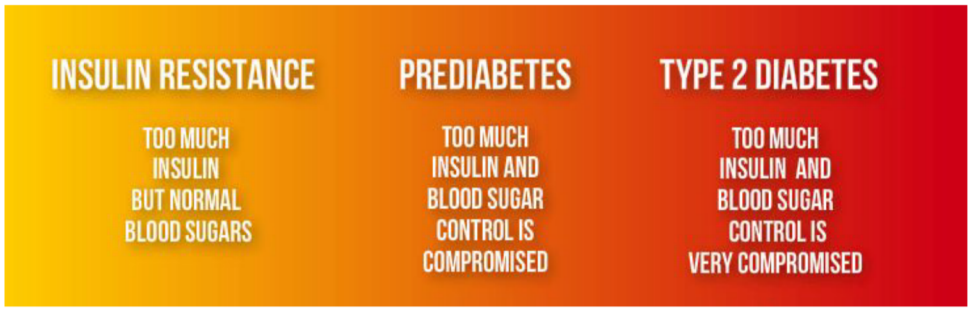
- "Allostatic load (AL) and overload are terms that represent degrees of **severity** of a **cumulative** effect of **stress** on the **body and brain**, and that acknowledge that the same mediators, when **overused and dysregulated relative** to each other, can be at the root of stress pathophysiology"
- AL can lead to mood disorders and dementia, among other conditions



Watson et al, Neuropharmacology, 2017.

What is Insulin Resistance (IR)?

- Reduced responsiveness of insulin-signaling pathways
- Risk factor for type II diabetes and dementia
- Reversible



Insulin resistance, an unmasked culprit in depressive disorders: Promises for interventions

Kathleen Watson [a, c], Carla Nasca [b], Linn Aasly [a], Bruce McEwen [b], Natalie Rasgon [a]

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Highlights

- IR is a pathological proinflammatory state underlying neuropsychiatric and somatic diseases.
- IR is part of a cascade of allostatic load, which is mediated in the periphery and CNS.
- PPAR- γ receptors, glutamate, cortisol are among mediators of peripheral and central crosstalk underlying IR.

How Does IR Affect the Brain?

- Hippocampus:
  - Interconnected brain region implicated in many functions including episodic memory, regulating depression and anxiety, and visuospatial navigation
- IR may have adverse effects on a dendritic spine and synapse formation in the hippocampus
  - Structurally and functionally

"I'm trying to Google what I was thinking about twenty minutes ago."

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Hippocampal volume reduction is associated with direct measure of insulin resistance in adults

Sophia Frangou [a, b], Fahim Abbasi [c], Katie Watson [d], Shalaila S. Haas [a], Mathilde Antoniades [a], Amirhossein Modabbernia [a], Alison Myoraku [d], Thalia Robakis [a], Natalie Rasgon [d]

- Cohort:
  - N=104
  - Ages: 23-61
  - Overweight and obese adults (BMI between 25-35)
- Data collected:
  - Steady state plasma glucose (SSPG) test
  - Imaging: structural MRI (sMRI) for hippocampal volume
  - Other variables: fasting insulin, glucose, leptin, BMI, adiposity
- Statistics:
  - K-means clustering: unsupervised machine learning method
  - Used variables listed above to identify two different clusters of individuals

IR Associated with Smaller Hippocampal Volume

- K-means identified two clusters
- Adiposity, insulin resistance and compromised structural hippocampal integrity behave as a composite phenotype
- Female sex as risk factor for this phenotype

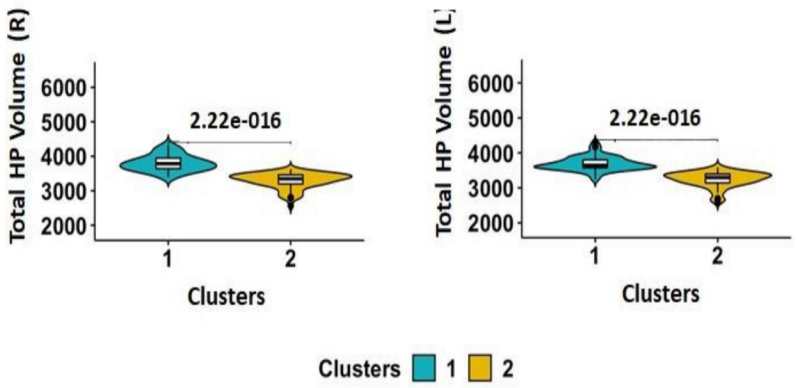


Figure: Violin plots depicting cluster differences in total hippocampal volume

Table 2
Sociodemographic and metabolic characteristics of the 2-cluster solution.

Variable	Cluster 1 (N = 49)	Cluster 2 (N = 65)	P-value
Female, N (%)	20 (42 %)	52 (79 %)	0.0001
Age, years	39.8 (8.5)	37.6 (8.6)	0.18
White, N (%)	30 (61 %)	30 (46 %)	
Black, N (%)	17 (35 %)	18 (28 %)	0.11
Other race/ethnicity, N (%)	2 (4%)	17 (26 %)	
Year of education	18.33 (4.44)	16.48 (4.38)	0.03
Waist circumference, m	0.96 (0.08)	0.99 (0.12)	0.20
BMI, kg/m^2	**27.9 (2.5)**	**30.5 (4.6)**	**0.0002**
Normal weight, N (%)	7 (14 %)	7 (11 %)	
Overweight, N (%)	34 (69 %)	25 (38 %)	0.0006
Obese, N (%)	8 (16 %)	33 (51 %)	
SSPG, mg/dL	**123 (61)**	**156 (70)**	**0.008**
Fasting insulin, mU/L	9.0 (3.8)	10.8 (7)	0.08
Fasting glucose, mg/dL	89 (8)	92 (10)	0.07
Leptin, µg/L	**21.7 (17.0)**	**44.5 (30.4)**	**1.70E-06**
Cortisol, µg/dL	9.0 (4.7)	9.0 (4.5)	0.98

Continuous data are shown as mean (standard deviation) and categorical data as number (percentage); BMI-body mass index; SSPG- steady-state plasma glucose; Bold font indicates significant results at P<0.05 with False Discovery rate correction.

European Psychiatry

Eur Psychiatry. 2022; 65(1): e29.
Published online 2022 May 2. doi: 10.1192/j.eurpsy.2022.21

PMCID: PMC9158395
PMID: 35492025

Lower functional hippocampal connectivity in healthy adults is jointly associated with higher levels of leptin and insulin resistance

Shalaila S. Haas, [1] Alison Myoraku, [2] Kathleen Watson, [2] Thalia Robakis, [1] Sophia Frangou, [1, 3] Fahim Abbasi, [4] and Natalie Rasgon [2,*]

- Cohort same as previous study
- Data:
  - Hippocampal connectivity data measured from functional MRI (fMRI)
    - Cohesiveness vs integration
  - Wechsler Abbreviated Scale of Intelligence (WASI) – general measure of cognition
  - Digit Symbol Pairing and Digit Symbol Free Recall – episodic memory
- Statistics:
  - K-means clustering

IR associated with lower cohesiveness in hippocampus

- K-means clustering identified two groups
- Lower cohesiveness and integration in group with greater metabolic deviance
- May be regulated by leptin
- Clusters did not differ by general intellectual ability or episodic memory

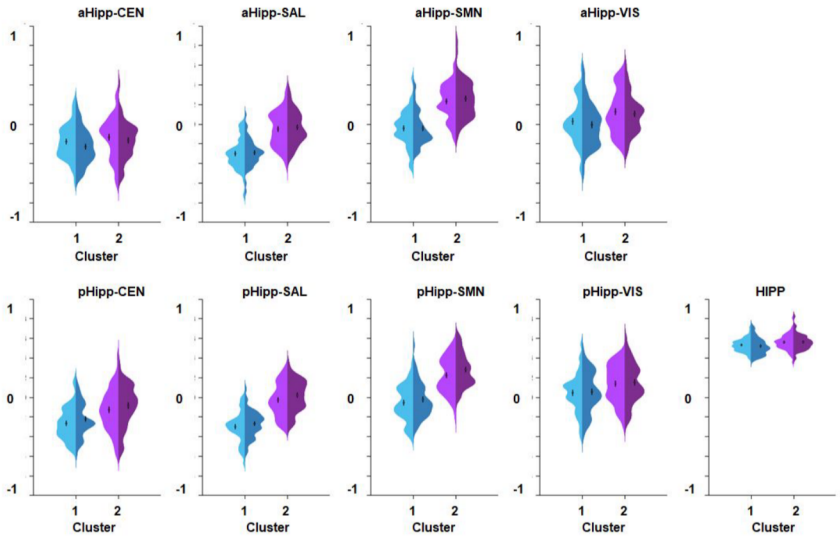
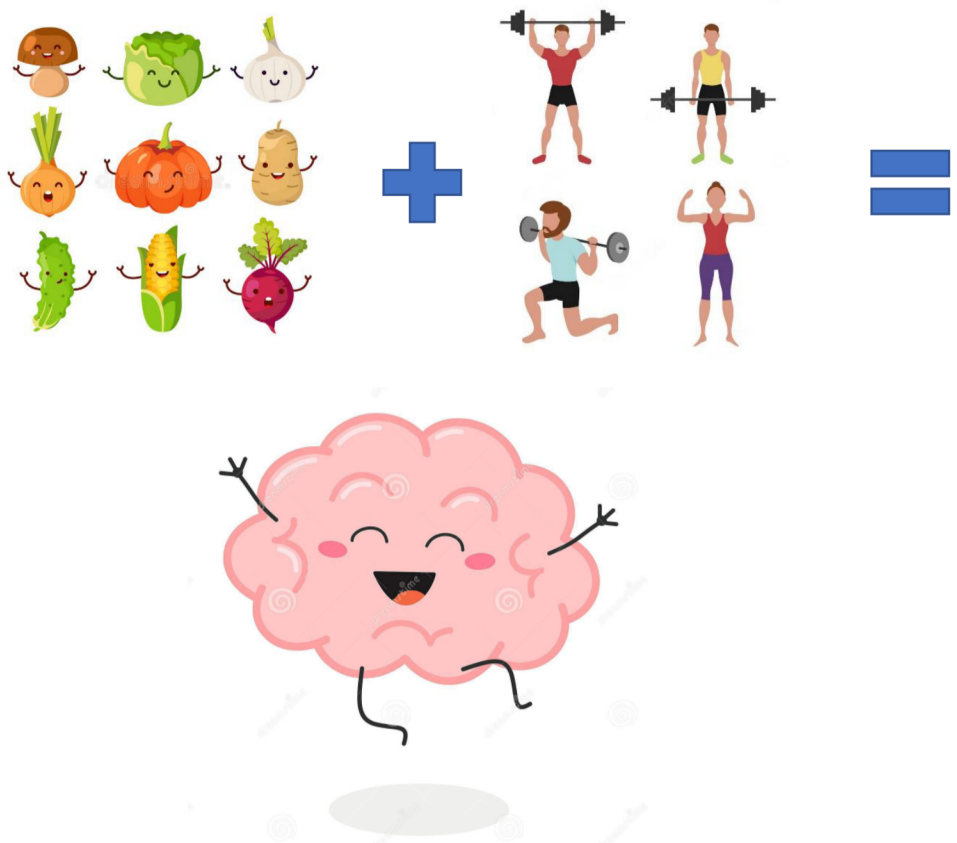


Figure: Lower functional cohesiveness and integration of the hippocampus in metabolically challenged individuals

Take Home Messages

- Insulin resistance is associated with changes in the brain (both structural and functional) in adults without any psychiatric/somatic illnesses (with exception of overweight/obese)
- Identifying associations early in the life and/or disease course is key
- Insulin resistance is modifiable!



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