The Genetics of PTSD-Related Accelerated Aging

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Boston University School of Medicine, Department of Psychiatry

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  - Harvard School of Public Health/Channing: Immaculata De Vivo & Patrice Soule
  - Research Assistants: Tawni Stoop, Hannah Maniates, Emily Sperbeck

The New York Times

HEALTH

Leading a Nation Takes Years Off Life, Study Suggests

By LAWRENCE K. ALTMAN DEC. 14, 2015

President Obama and Mitt Romney at the end of a presidential debate in October 2012. A study found elected heads of government lived fewer years than the candidates they defeated. Pablo Martinez Monsivais/Associated Press

Well

PHYS ED

What's Your Fitness Age?

By GRETCHEN REYNOLDS OCTOBER 15, 2014 12:01 AM 141 Comments

Getty Images

Email

You already know your chronological ag
fitness age?

Well

PHYS ED

Does Exercise Slow the Aging Process?

By GRETCHEN REYNOLDS OCTOBER 28, 2015 5:45 AM 175 Comments

"You're fifty-seven years old. I'd like to get that down a bit."

PTSD and Accelerated Aging

- Chronic PTSD symptoms as an emotional & physio stressor (Miller & Sadeh, 2014)
- Associated with premature morbidity (e.g., Miller & Sadeh, 2014; Lohr et al., 2015)
  - Early onset of cardiovascular, metabolic, autoimmune, and neurological problems, and possibly, early death (e.g., Schnurr et al., 2000; Wolf et al., 2016; Lohr et al., 2015)
- Chronic PTSD may accelerate aging at cellular level
  - PTSD associated with shortened telomere length (Ergodic et al., 2014; Tyra et al., 2015; Zhang et al., 2014)

DNAm Age

- Recent discoveries suggest DNA methylation (DNAm) is strongly related to chronological age
  - Hannum et al., 2013: 71 DNAm loci in whole blood (r = .96 w/ chron age)
  - Horvath, 2013: 353 DNAm loci from multiple tissues (r = .96 w/ chron age)
- Predictors of DNAm age > chron age
  - Obesity (in liver tissue; Horvath et al., 2014)
  - Alcohol use (Weidner et al., 2014)
  - Financial stress (Simons et al., 2016)
- Correlates of DNAm age > chron age
  - Frailty (Breitling et al., 2016)
  - Worse performance on cognitive, motoric, and lung function tasks (Marion et al., 2015)
  - Increased risk for mortality
    - Δ 5yrs = 21% (Hannum) and 11% (Horvath) increase in all-cause mortality (Marion et al., 2015)
    - Horvath & Hannum DNAm age + white blood cell composition predicted death and time to death (Horvath et al., 2016)
    - Horvath DNAm age predicted cancer-related deaths specifically: Δ 5yrs = 1.20 hazard ratio (Zhang et al., 2016)

Trauma, PTSD, and DNAm Age

- One prior longitudinal study (Boks et al., 2015)
  - Trauma associated with accelerated Horvath DNAm age
  - PTSD associated with decelerated Horvath DNAm age
  - No control for chronological age
- Life stressors, but not child trauma or PTSD, associated with accelerated Horvath DNAm age (Zannas et al., 2015)
  - Effect greater in relatively older subjects
  - Evidence for glucocorticoid regulation of the pace of cellular aging
    - 24% of Horvath loci located in glucocorticoid response elements
    - 31% of DNAm loci were responsive to dexamethasone
    - 82% of genes near the Horvath loci showed expression changes in response to dex

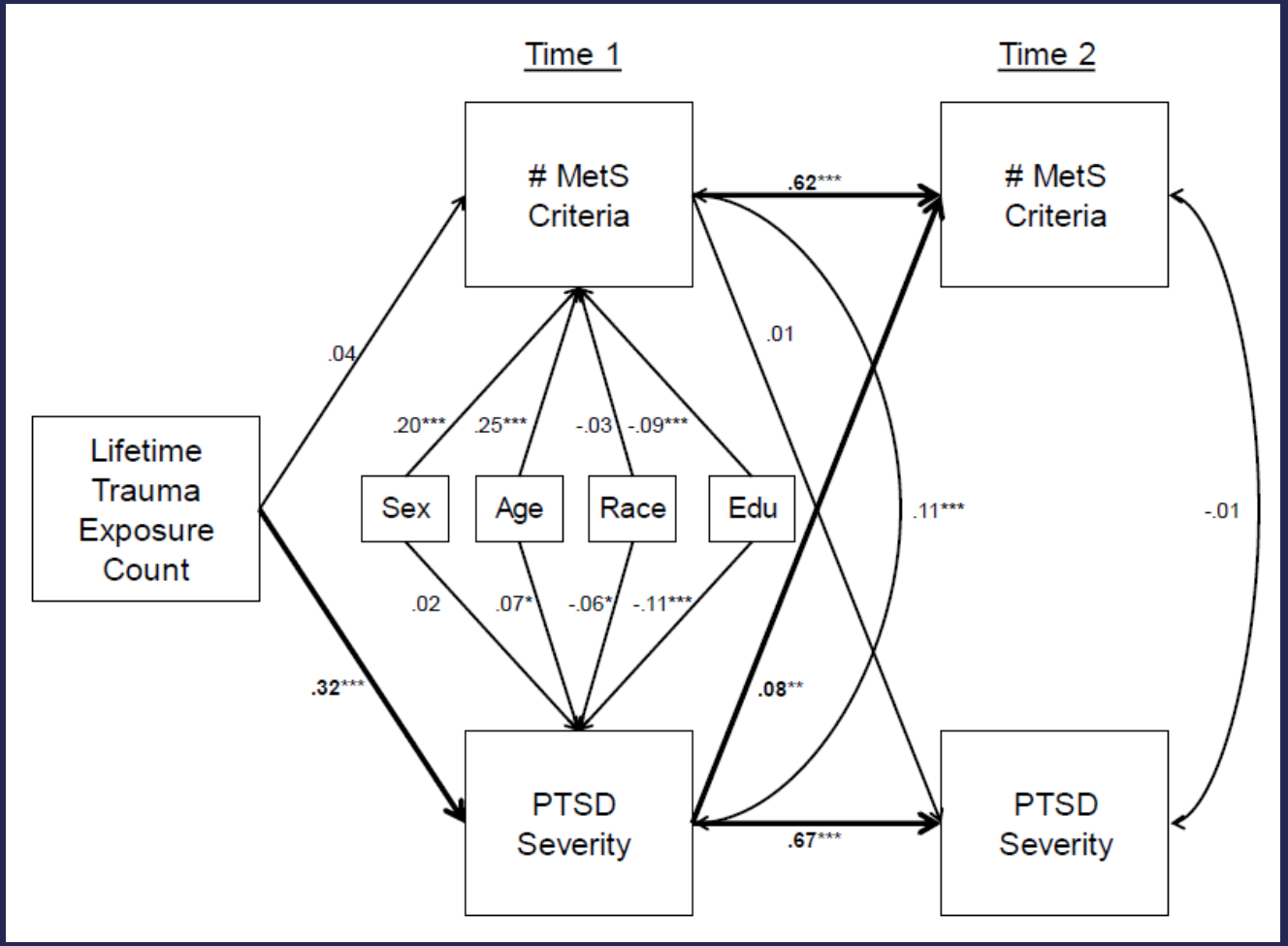
Metabolic Syndrome (MetS)

- Constellation of Symptoms
  - Obesity
    - Waist-to-hip ratio > 102cm (men)/88cm (women)
  - Elevated blood pressure
    - Systolic ≥ 130 mmHg
    - Diastolic ≥ 85 mmHg
  - Insulin resistance
    - Fasting glucose ≥110 mg/DL
  - Dyslipidemia
    - HDL < 40 mg/dL (men)/50 mg/dL (women)
    - Triglycerides ≥ 150 mg/dL
- Very costly: $80 billion in US (Sullivan et al., 2007)

National Cholesterol Education Program Adult Treatment Panel III

PTSD and MetS

- ~40% of those with PTSD meet criteria for MetS (Rosenbaum et al., 2015; Bartoli et al., 2013)
- 2X the risk of population controls (Rosenbaum et al., 2015)
- PTSD predicts increasing MetS risk over time (Wolf et al., 2016)
- MetS as a clinical manifestation of PTSD-related accelerated aging



Wolf et al., 2016 in *Psychological Medicine*

Potential Pathways Linking PTSD to Accelerated Aging

- Biological pathways
  - HPA axis reactivity
  - Autonomic reactivity
  - Immune system dysregulation & inflammation
  - Oxidative stress
- Behavioral pathways
  - Poor sleep
  - Insufficient exercise (sedentary lifestyle)
  - Poor nutrition (increased fat and simple sugar consumption)
  - Cigarette and alcohol use
- Collectively degrade cellular integrity, induce metabolic dysregulation, and promote cell death

G & E Risk Factors and G X E

Epigenetic Biomarkers & Mechanisms of Accelerated Aging

Clinical Manifestations of Accelerated Aging

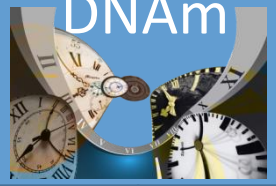
Chronic PTSD Symptoms

Genotype

moderation

Health behaviors & bio reactivity

Accelerated Cellular Aging DNAm



Health behaviors & bio reactivity

Neurocognitive Decline

Metabolic & CVD Disease

Early Death

Chrono-logical Aging

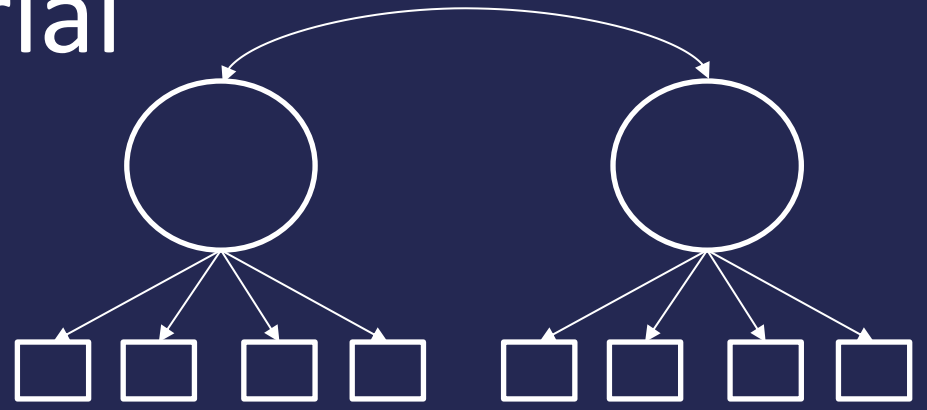
Methods: Returning Veterans

- 281 OIF/OEF veterans in TRACTS protocol
  - 88% male
  - Mean age: 32 years (range: 19 – 58)
  - 70.5% White, 15.3% Hispanic or Latino/a, 8.5% Black or African American
- Assessed for PTSD with the CAPS for three periods of time
  - current, post-military, pre-military
  - ~75% Lifetime PTSD
- Metabolic syndrome components assessed
- DNA extracted from whole blood
  - DNA completed via Illumina 2.5 mill array & more SNPs imputed via IMPUTE2
  - DNAm completed via Illumina 450k beadchip
  - PCs and substructure PCs estimated based on 100,000 SNPs
  - WBCs estimated from DNAm data using Houseman method
  - DNAm age calculated per Horvath & Hannum et al. algorithms
    - DNAm age residuals → regress chronological age from DNAm age
- Neuroimaging parameters for subset of 200-241 participants

Methods: Mixed Era Veterans

- N = 464 White, non-Hispanic trauma-exposed veterans (n = 319) and their trauma exposed partners (n = 145)
- 64.7% male
- Mean age: 52 yrs (SD: 10.65), range: 23-75 yrs
- Administered current and lifetime CAPS & SCID
- Blood drawn for DNA and DNAm
- Lifetime PTSD: ~60%
- Beadchips, calculation of DNAm age, WBCs, and PCs as with prior sample

Quick SEM Tutorial



- Latent variables/Confirmatory Factor Models
  - Important for phenotype refinement
  - Denoted by circles
  - Reflect construct underlying observed variables (squares)
  - Capture variance in common across observed variables
  - Separate “true” score variance from error variance
  - Fit stats to determine they adequately represent the data
  - Improved reliability, construct validity, statistical power
- Structural Equation/Path Models
  - Single-headed arrows = regressive paths
  - Double-headed arrows = correlations
  - Fit stats

G, E and G X E Risk Factors

Epigenetic Biomarkers & Mechanisms of Accelerated Aging

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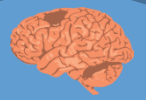

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Accelerated DNA methylation age: Associations with PTSD and neural integrity

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ABSTRACT

Background: Accumulating evidence suggests that posttraumatic stress disorder (PTSD) may accelerate cellular aging and lead to premature morbidity and neurocognitive decline.
Methods: This study evaluated associations between PTSD and DNA methylation (DNAm) age using recently developed algorithms of cellular age by Horvath (2013) and Hannum et al. (2013). These estimates reflect accelerated aging when they exceed chronological age. We also examined if accelerated cellular age manifested in degraded neural integrity, indexed via diffusion tensor imaging.
Results: Among 281 male and female veterans of the conflicts in Iraq and Afghanistan, DNAm age was strongly related to chronological age ($rs \sim .88$). Lifetime PTSD severity was associated with Hannum DNAm age estimates residualized for chronological age ($\beta = .13$, $p = .032$). Advanced DNAm age was associated with reduced integrity in the genu of the corpus callosum ($\beta = -.17$, $p = .009$) and indirectly linked to poorer working memory performance via this region (indirect $\beta = -.05$, $p = .029$). Horvath DNAm age estimates were not associated with PTSD or neural integrity.
Conclusions: Results provide novel support for PTSD-related accelerated aging in DNAm and extend the evidence base of known DNAm age correlates to the domains of neural integrity and cognition.
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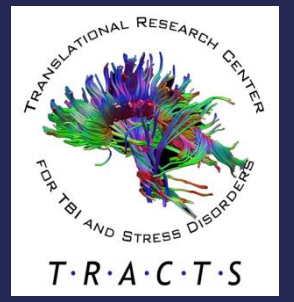
PTSD and DNAm Age: TRACTS Sample

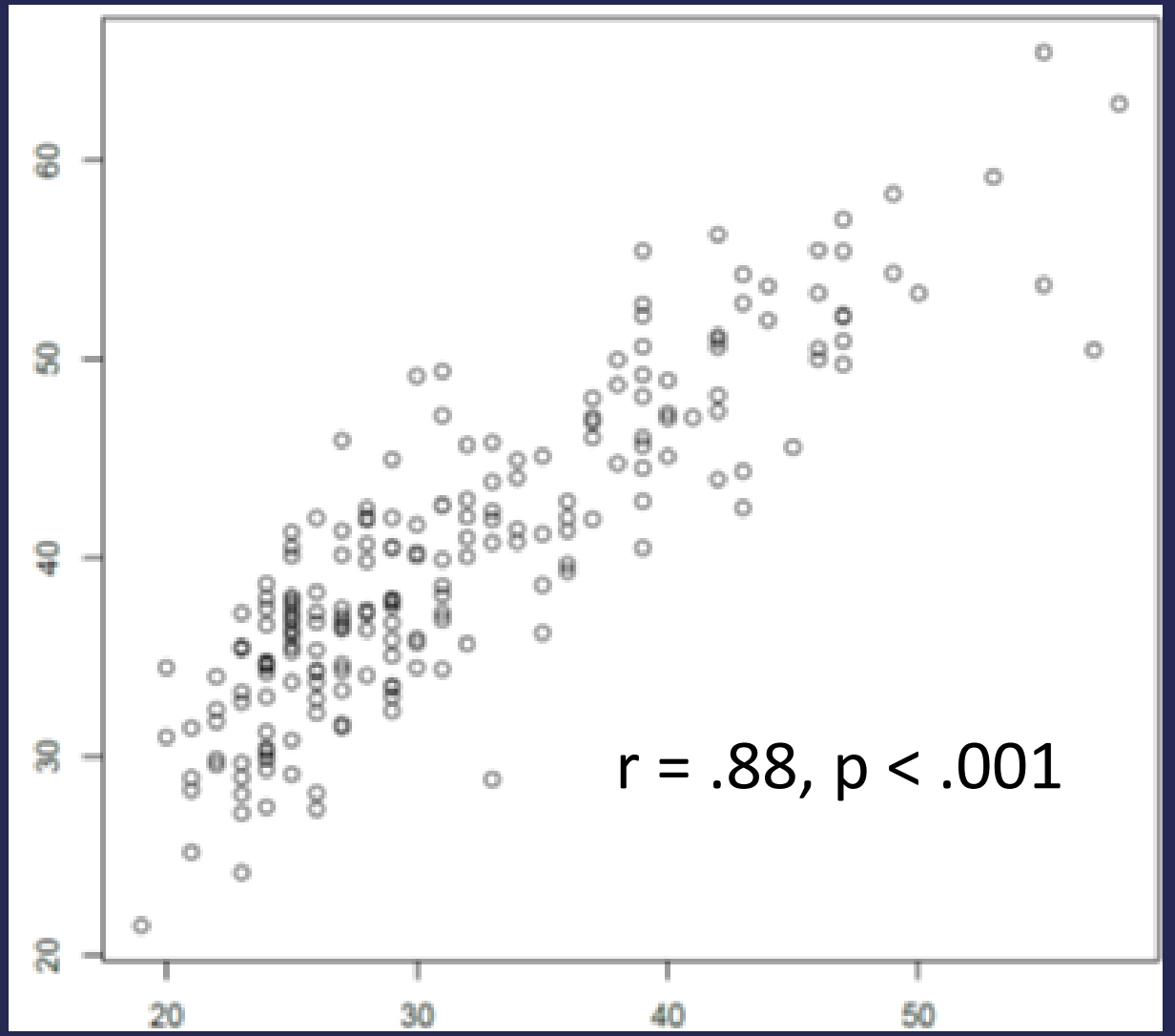


- Evaluate associations between PTSD and DNAm age, controlling for chronological age
- Examine if accelerated DNAm age is reflected in decreased neural integrity (DTI) in regions known to be sensitive to age (Salat et al., 2005)
  - frontal cortices
  - genu of the corpus callosum
    - Connects R&L dorsolateral prefrontal cortices
    - Developmentally late myelinating region with high metabolic requirements
    - Critical for executive functions and working memory
- Examine if accelerated DNAm age is indirectly linked to poorer performance on cognitive tests via decreased microstructural integrity
- Examine if accelerated DNAm age is related to metabolic syndrome

DNAm Age and Chronological Age

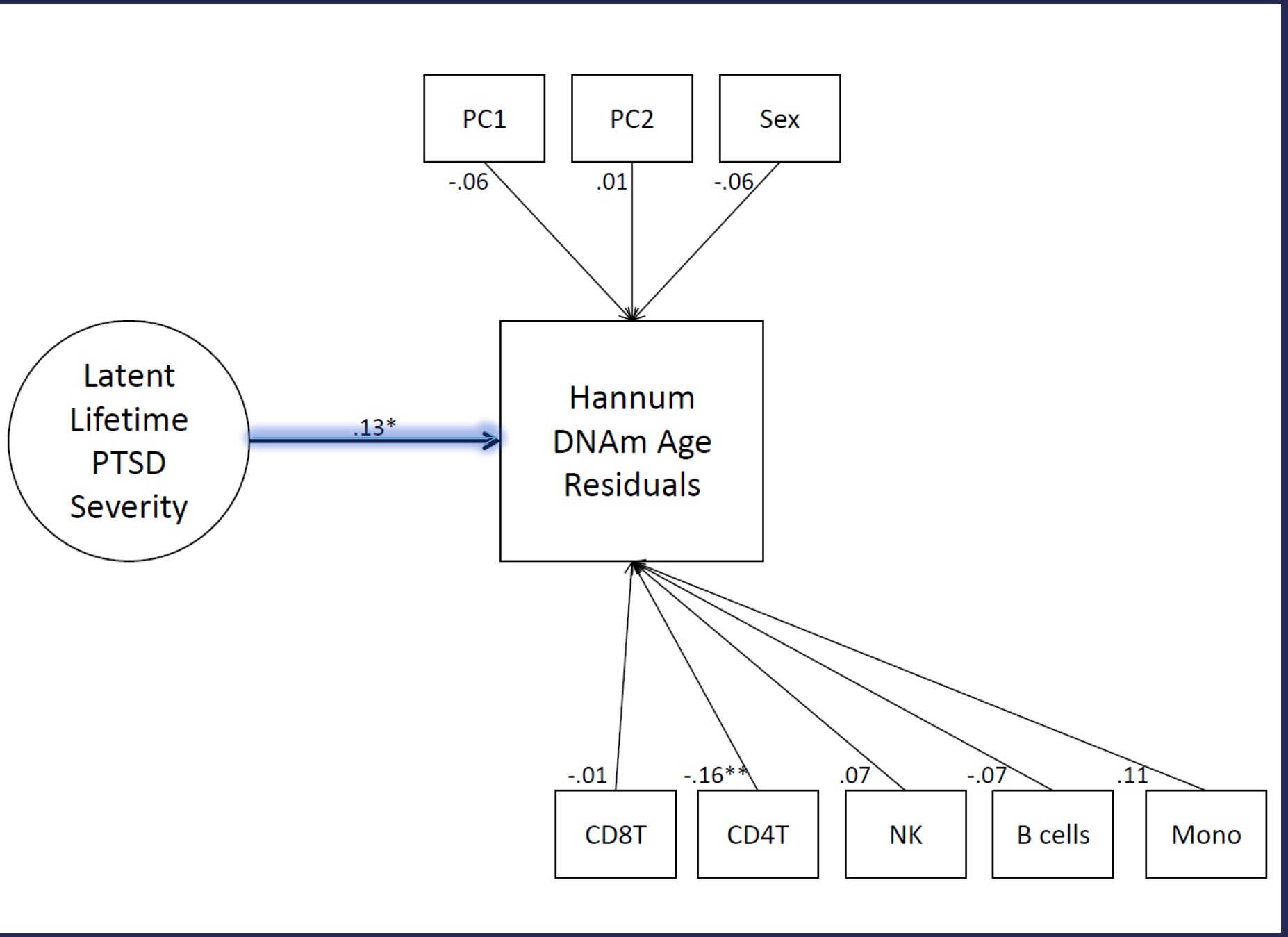
r Hannum & Horvath = .88

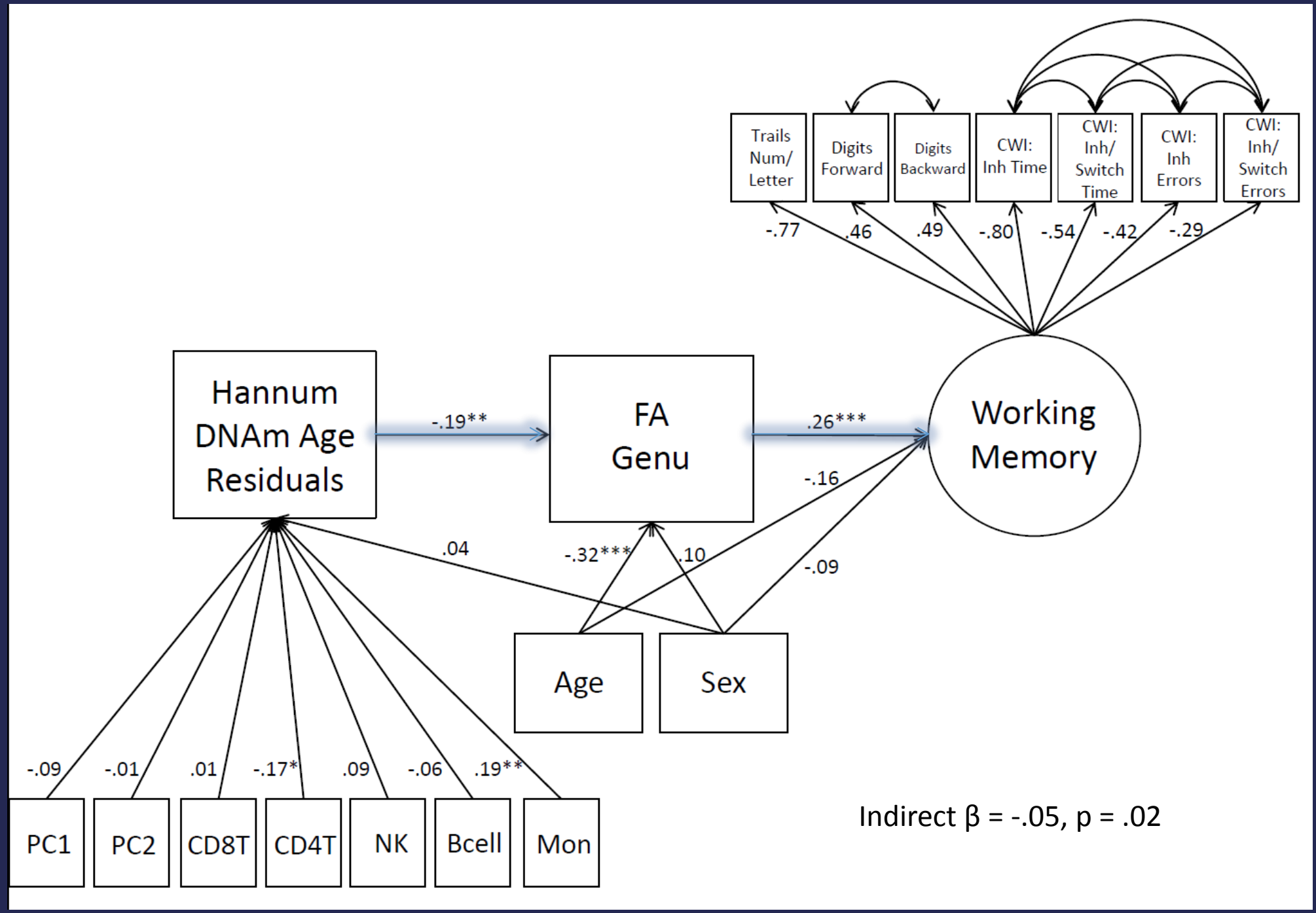
r Hannum & Horvath residuals = .49



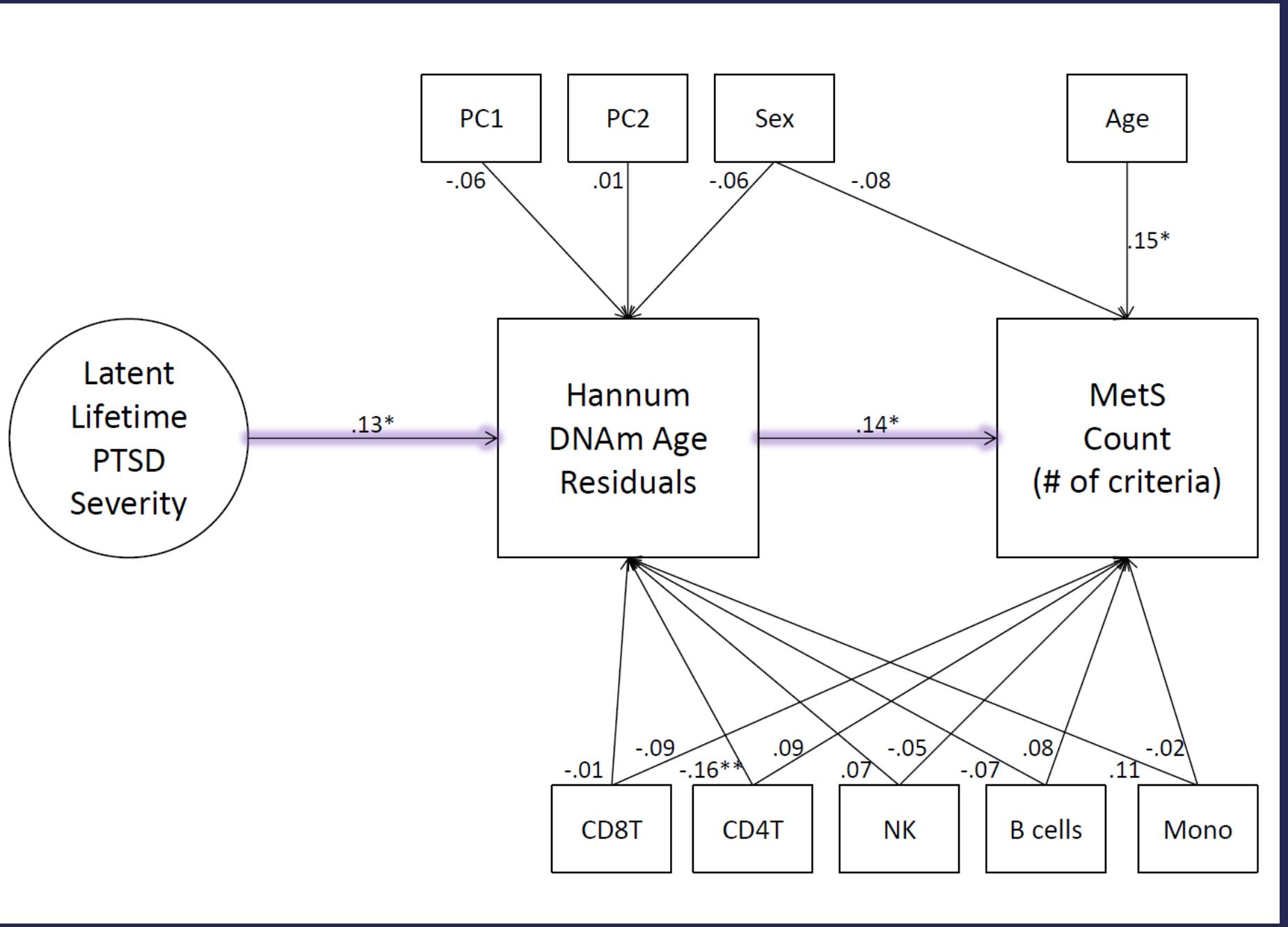
Hannum age residuals:
−11.82 to 19.24 years
M = .05, SD = 4.25

Horvath age residuals:
−13.04 to 16.90 years
M = .03, SD = 3.81


PC1
PC2
Sex
-.06
.01
-.06
Latent Lifetime PTSD Severity
.13*
Hannum DNAm Age Residuals
-.01
-.16**
.07
-.07
.11
CD8T
CD4T
NK
B cells
Mono



Indirect β = -.05, p = .02

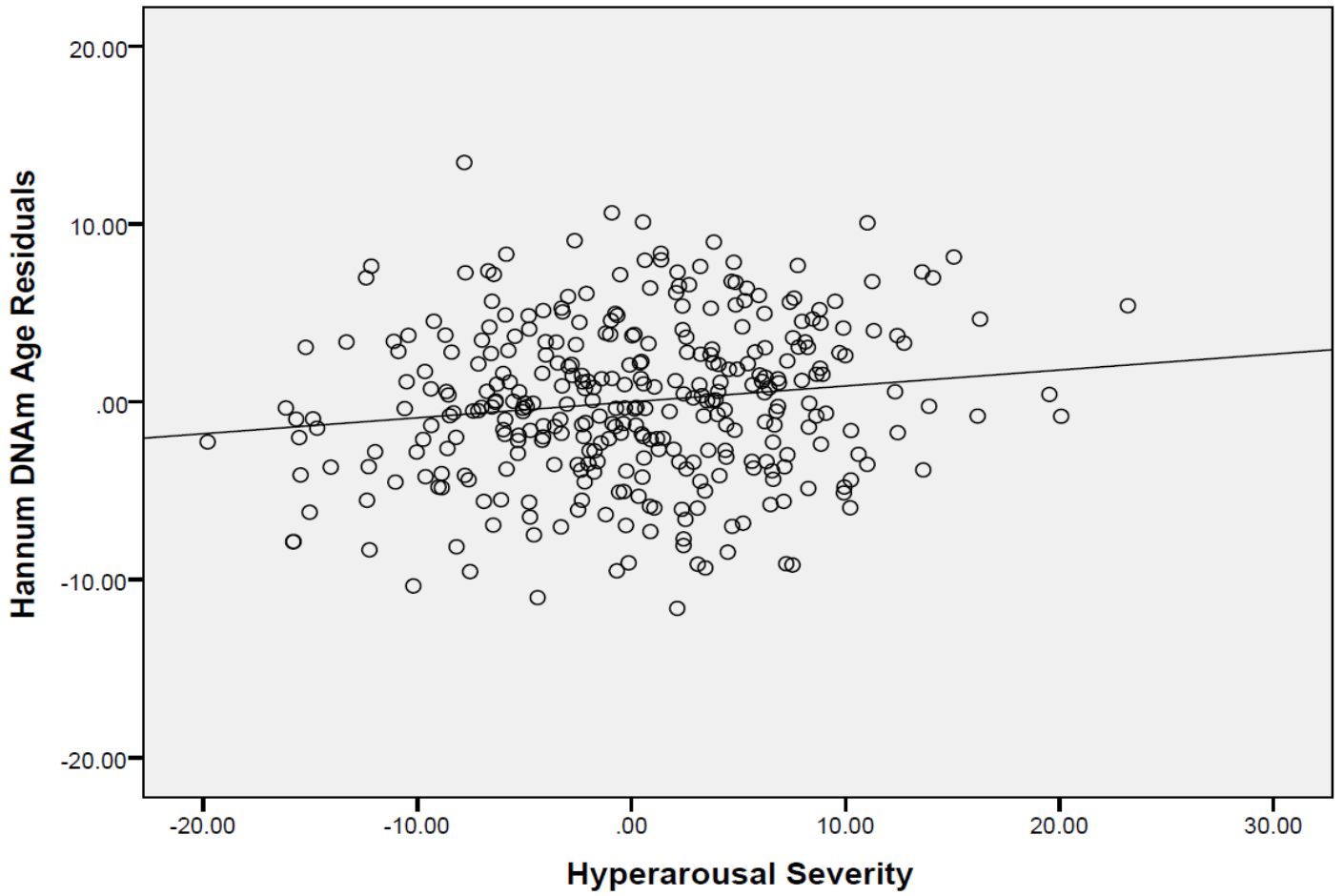

PC1
PC2
Sex
Age
-.06
.01
-.06
-.08
.15*
Latent Lifetime PTSD Severity
.13*
Hannum DNAm Age Residuals
.14*
MetS Count (# of criteria)
-.01
-.09
-.16**
.09
.07
-.05
-.07
.08
.11
-.02
CD8T
CD4T
NK
B cells
Mono

PTSD and DNAm Age: Mixed-Era Sample

- Extend work in TRACTS sample to middle-aged sample
  - Evaluate associations between PTSD and Hannum DNAm age, controlling for chronological age
  - Examine relative contribution of PTSD symptom clusters to DNAm age
    - Reexperiencing
    - Avoidance & Numbing
    - Hyperarousal
  - Examine if accelerated DNAm age predicts all-cause mortality
  - Examine associations between trauma, PTSD and telomere length
  - (This ms currently under review)

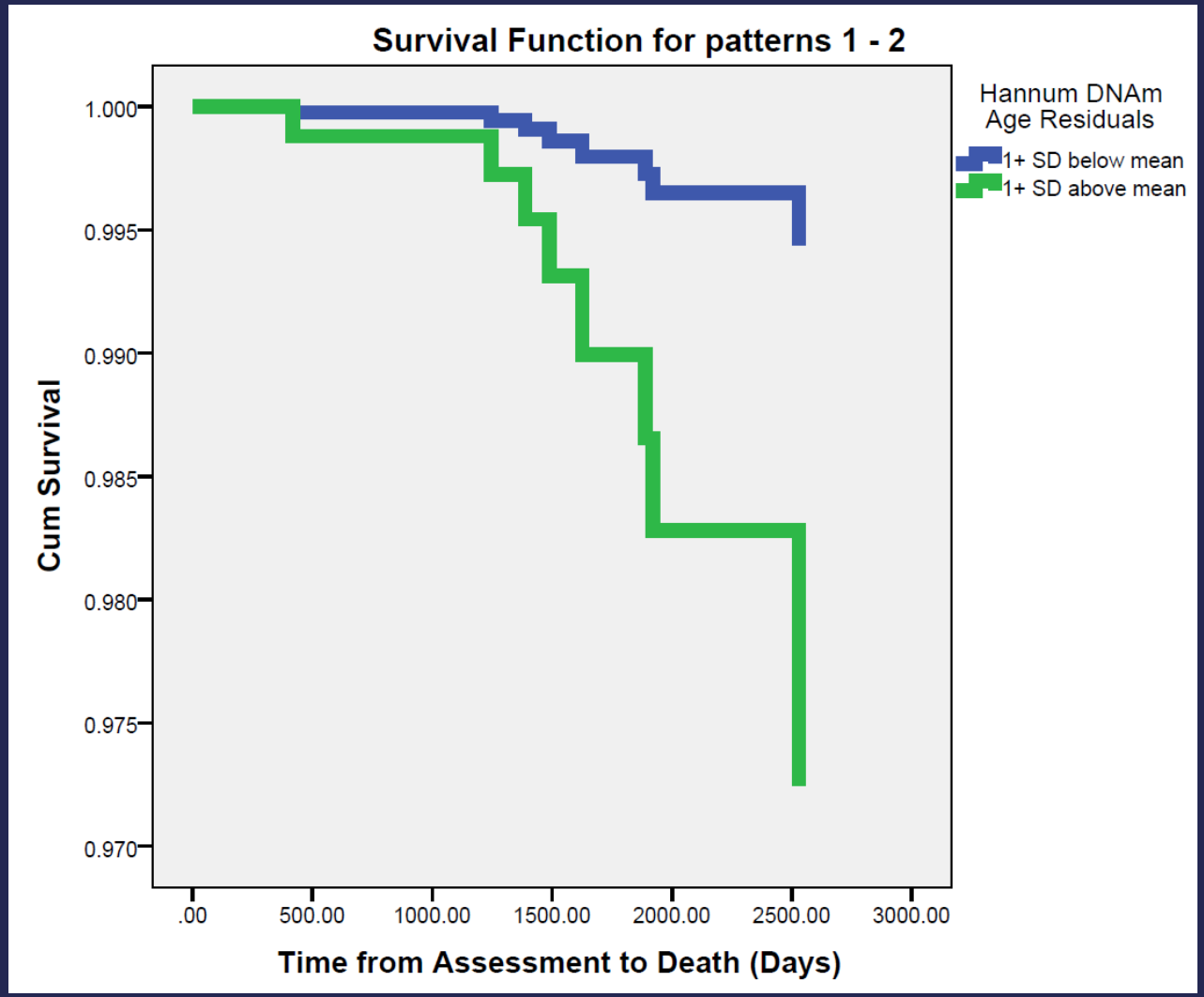
Results

- Hannum & Horvath DNAm age with age: *rs* = .89/.90
- Men showed greater Hannum DNAm age residuals relative to women
- In the full sample, effects for
  - Trauma exposure: β = .10, p = .049
  - Hyperarousal Sx: β = .14, p = .046
- In the veterans, effects for:
  - Hyperarousal Sx: β = .20, p = .009



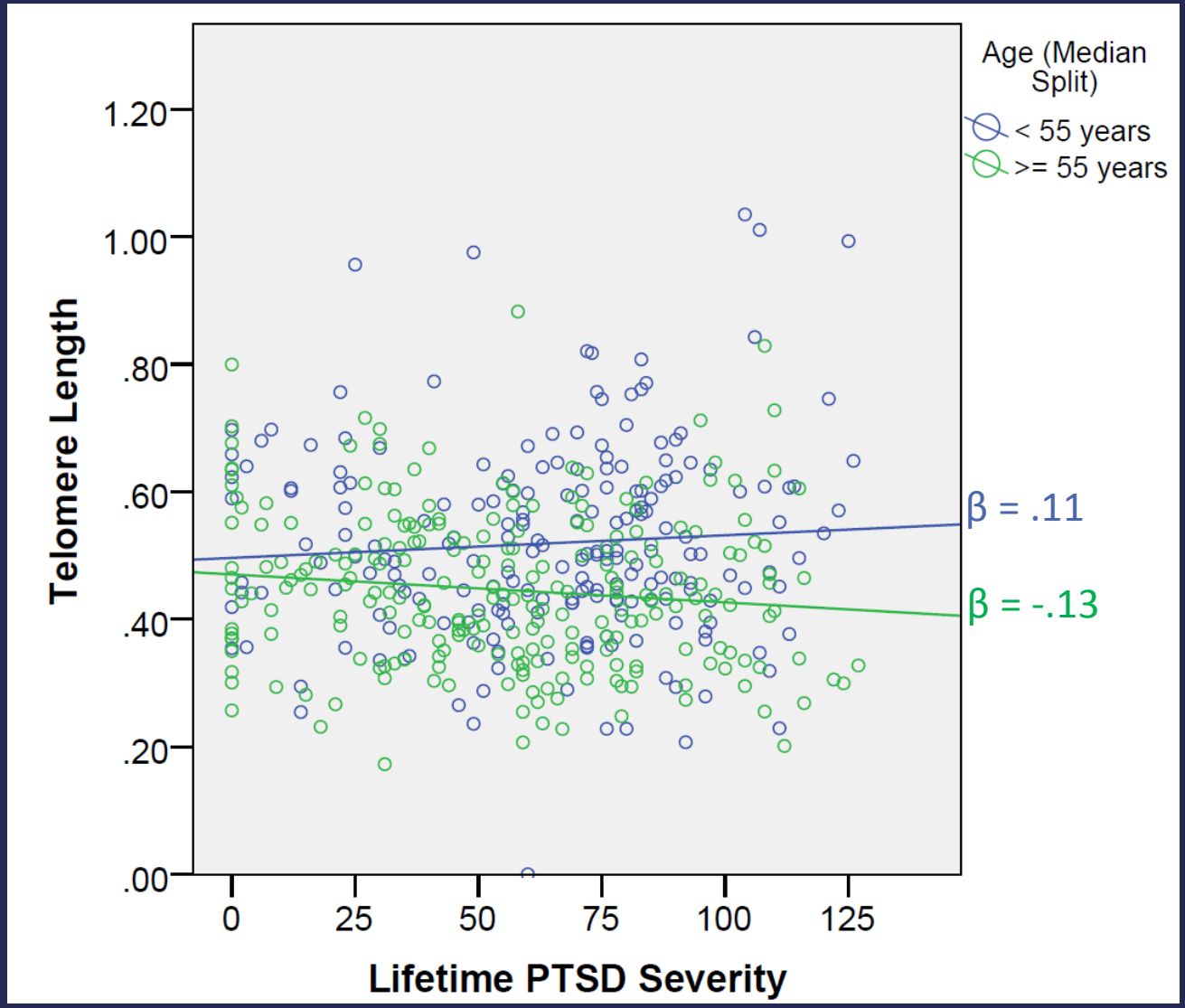
Accelerated DNAm Age and Mortality

- N = 241 veterans with medical record data
  - 17 (7%) died prior to our follow-up in 8/2015 (followed approx 6.5 yrs)
- Survival curve
  - Controlled for PCs, WBCs, age, sex, PTSD
  - Accelerated DNAm Age associated with 1.13 (95% CI: 1.01 to 1.26) increased odds of death
  - On average, those who died had approx 3 year greater age acceleration
  - On average, those who died, did so about 3.5 years after assessment



Telomere Length and PTSD

- Relationship between age and telomere length r ≈ .3
- No main effect of trauma or PTSD on telomere length
- Significant PTSD X Age effect: β = -.83, p = .001
  - Controlling for: PCs, age, sex, white blood cell counts, trauma
  - Lifetime PTSD severity associated with shorter telomere length among older subjects



Trauma, PTSD, and DNAm Age Meta-Analysis

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G, E and G X E Risk Factors

Epigenetic Biomarkers & Mechanisms of Accelerated Aging

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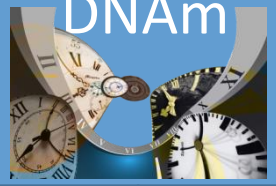
Accelerated Cellular Aging DNAm



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Archival Report

Biological Psychiatry

Posttraumatic Stress Disorder as a Catalyst for the Association Between Metabolic Syndrome and Reduced Cortical Thickness

Erika J. Wolf, Naomi Sadeh, Elizabeth C. Leritz, Mark W. Logue, Tawni B. Stoop, Regina McGlinchey, William Milberg, and Mark W. Miller

ABSTRACT

BACKGROUND: Metabolic syndrome (MetS), defined by a constellation of cardiometabolic pathologies, is highly prevalent among veterans, especially veterans with posttraumatic stress disorder (PTSD), and poses a major risk for adverse health outcomes, including neurodegeneration and mortality. Given this, we evaluated 1) the association between MetS and neural integrity, indexed by cortical thickness; 2) the relationship between PTSD and MetS; and 3) whether PTSD was associated with cortical thickness indirectly through MetS.

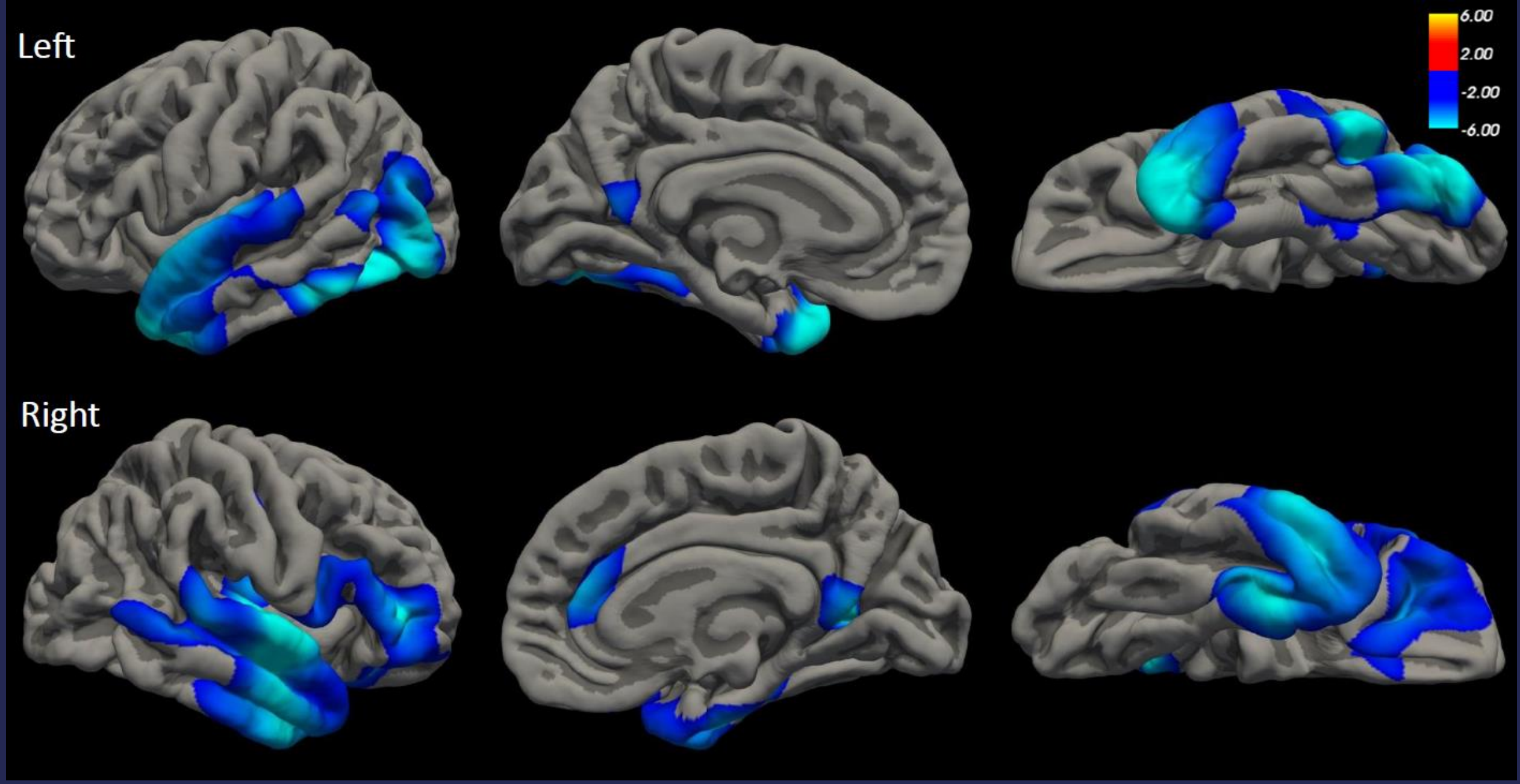
METHODS: The sample consisted of 346 US military veterans (89.3% male; 71.4% white) who deployed to Iraq, Afghanistan, or both. Neuroimaging data were available for 274 participants.

RESULTS: In whole-brain analyses, MetS was negatively associated with cortical thickness in two left and four right hemisphere regions, as follows: bilateral temporal lobe, including temporal pole, fusiform gyrus, and insula, and extending into occipital cortex (left hemisphere) and orbitofrontal cortex (right hemisphere); bilateral precuneus, posterior cingulate, calcarine, and occipital-parietal cortex; and right rostral anterior cingulate cortex and central sulcus/postcentral gyrus. Path models showed that PTSD predicted MetS ($\beta = .19$, $p < .001$), which was associated with reduced cortical thickness ($\beta = -.29$ to $-.43$, all $p < .001$).

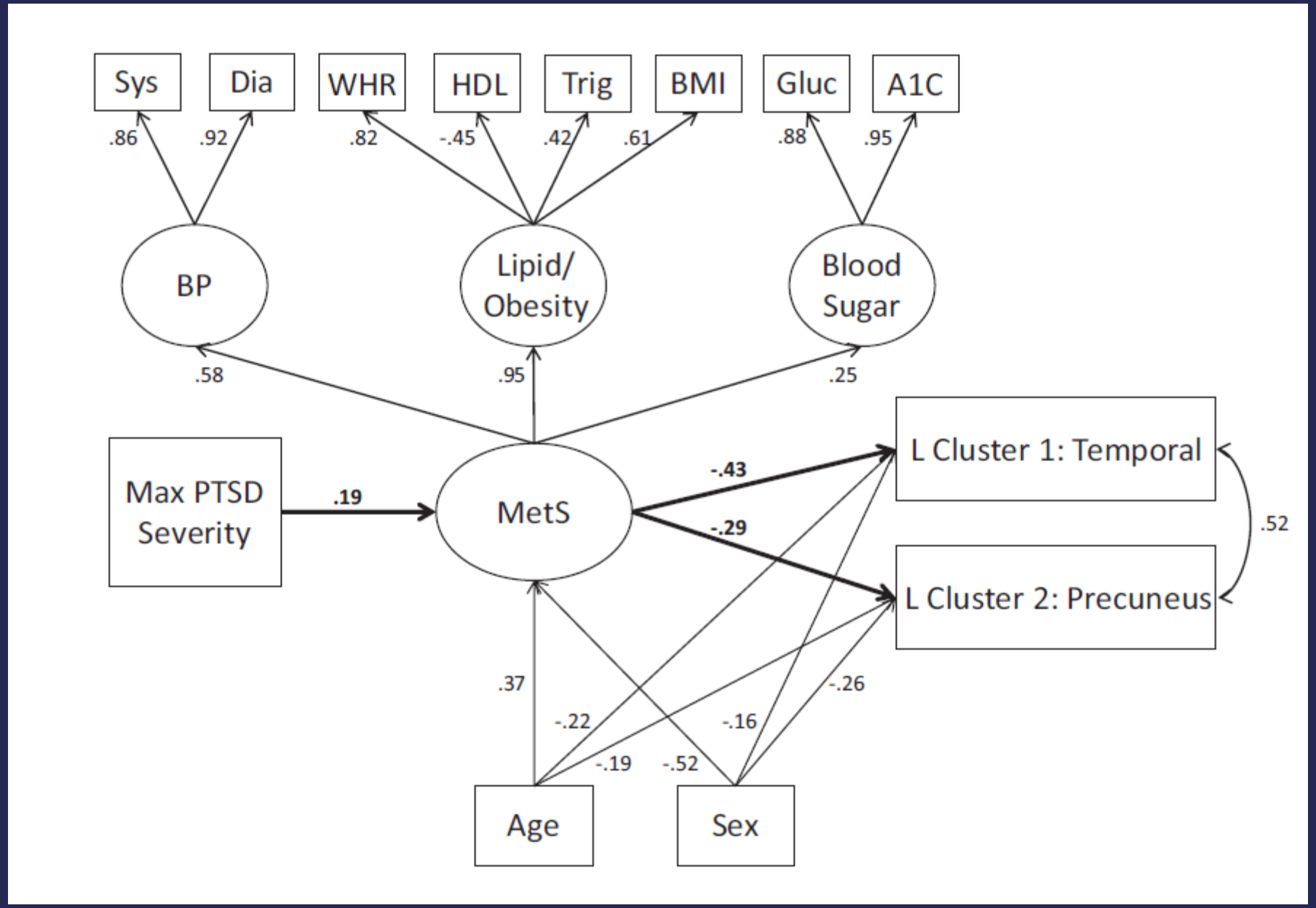
CONCLUSIONS: Results from this young veteran sample provide evidence that PTSD confers risk for cardiometabolic pathology and neurodegeneration and raise concern that this cohort may be aging prematurely and at risk for substantial medical and cognitive decline. This study highlights the need to identify the molecular mechanisms linking PTSD to MetS and effective interventions to reduce PTSD-related health comorbidities.

Keywords: Accelerated aging, Cortical thickness, Magnetic resonance imaging, Metabolic syndrome, Posttraumatic stress disorder, Structural equation modeling

http://dx.doi.org/10.1016/j.biopsych.2015.11.023



Wolf, E. J., Sadeh, N., Leritz, E., Logue, M. W., Stoop, T., McGlinchey, R., Milberg, W., & Miller, M. W. (2016). PTSD as a catalyst for the association between metabolic syndrome and reduced cortical thickness. *Biological Psychiatry*.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.95
BP
Lipid/
Obesity
Blood
Sugar
.58
.95
.25
Max PTSD
Severity
.19
MetS
-.43
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L Cluster 1: Temporal
L Cluster 2: Precuneus
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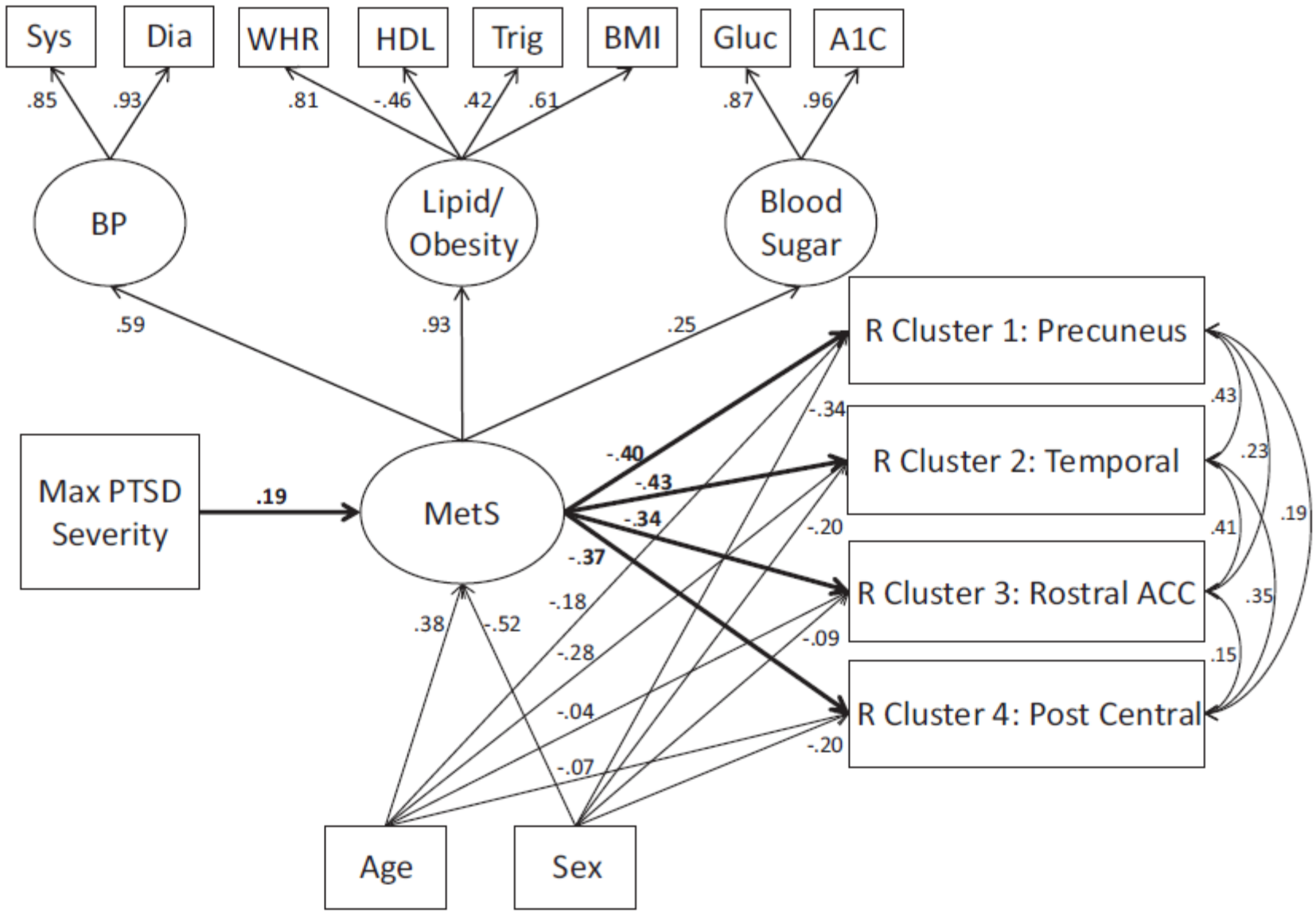
Age
Sex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Obesity
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Max PTSD
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-.37
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-.28
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-.07
.38
-.52
R Cluster 1: Precuneus
R Cluster 2: Temporal
R Cluster 3: Rostral ACC
R Cluster 4: Post Central
-.34
-.20
-.09
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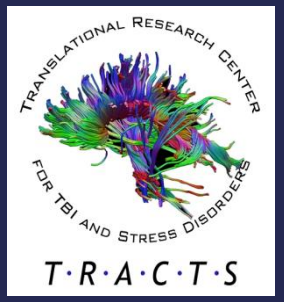
Age
Sex

PTSD, Polygenic Risk for Obesity, MetS, and Cortical Thickness



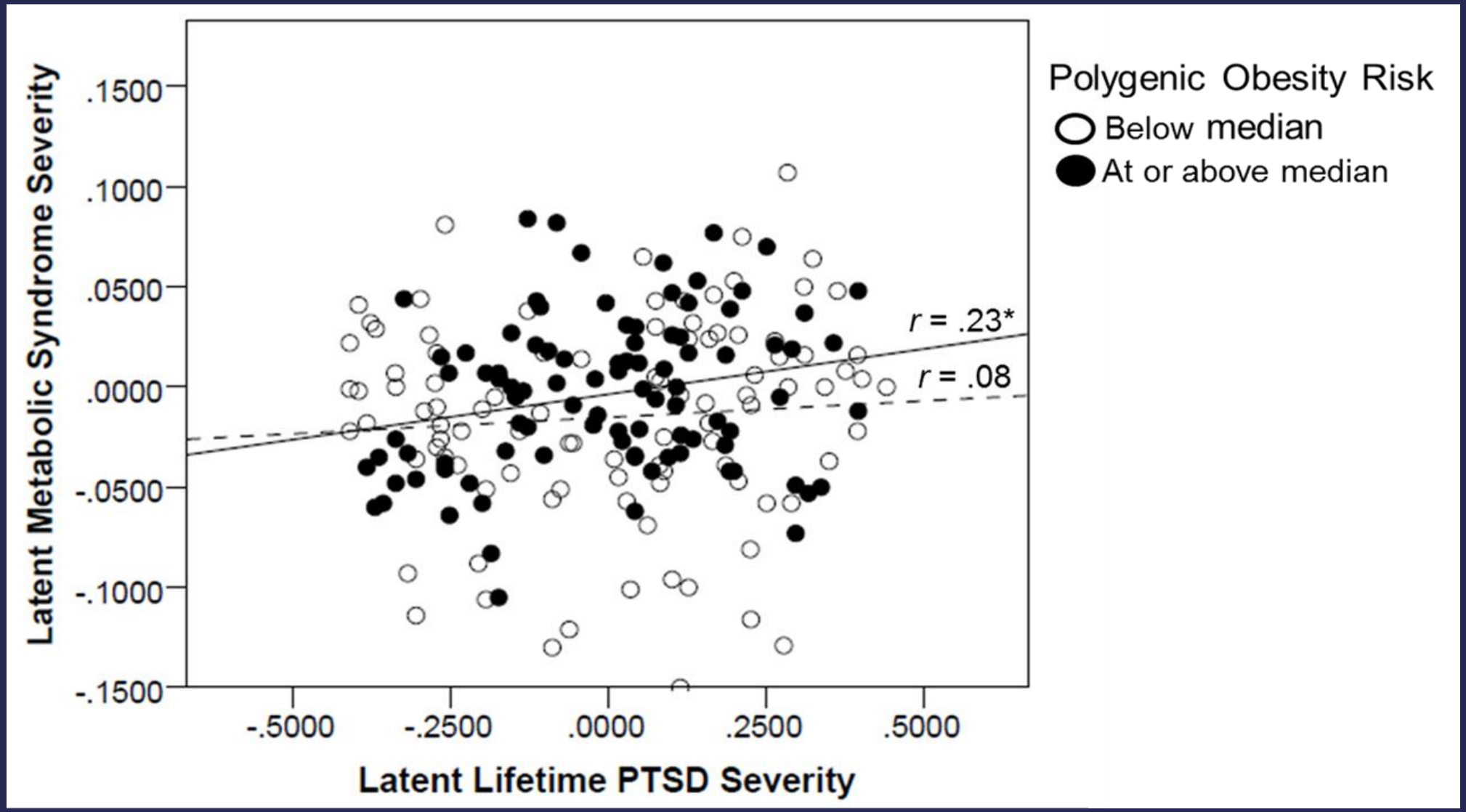
- Are effects of PTSD on MetS better accounted for by genetics?
  - Polygenic risk for obesity X PTSD → MetS
- Are effects of MetS on cortical thickness better accounted for by genetics?
  - Polygenic risk for obesity X MetS → Cortical Thickness
- (this ms under review)

- Obesity polygenic risk score
  - Generated from GWAS results of BMI in nearly 250k subjects (Speliotes et al., 2010; Nature Genetics)
    - GIANT Consortium data available at Broad Inst. website
  - Single score reflecting weighted associations between common variants across the genome and phenotype
  - All SNPs with p < .05 from GWAS included in risk score (n = 17,955)
    - Exclusions: ambiguous SNPs, MAF < 1%, poor imputation quality; SNPs clumped in local LD
- Latent MetS variable derived from raw lab values

Predicting Latent MetS

Model	Std. β	p	R^2
Main Effects			.453***
Age	.39	< .001	
Sex	-.57	< .001	
PC1	-.05	.36	
PC2	-.05	.42	
Trauma Exposure	.13	.032	
Latent Lifetime PTSD Sev	.17	.005	
Obesity PRS	.15	.009	
Interaction			.469***
Latent PTSD X Obesity PRS	.13	.02	

PTSD X Polygenic Obesity Risk

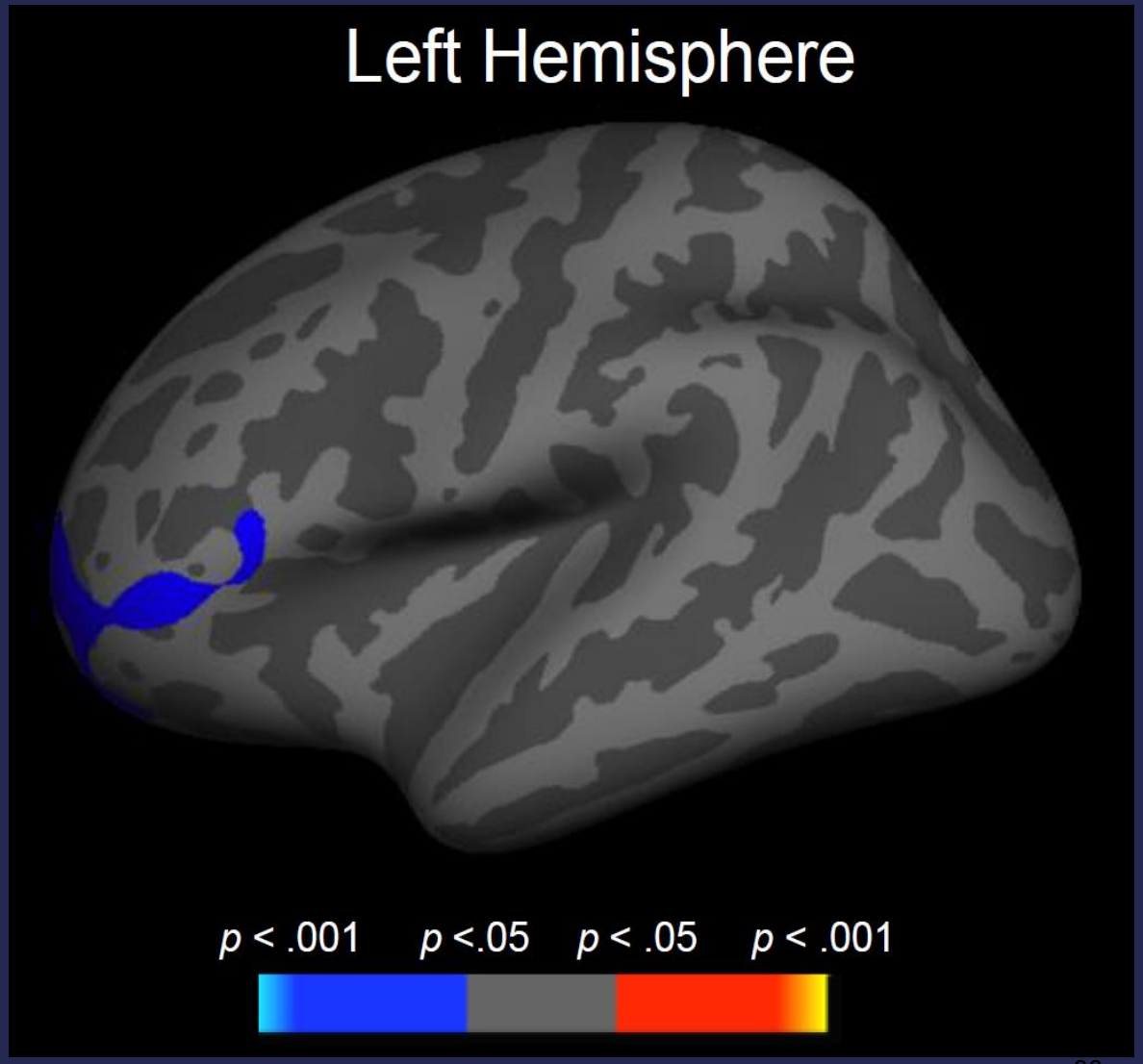


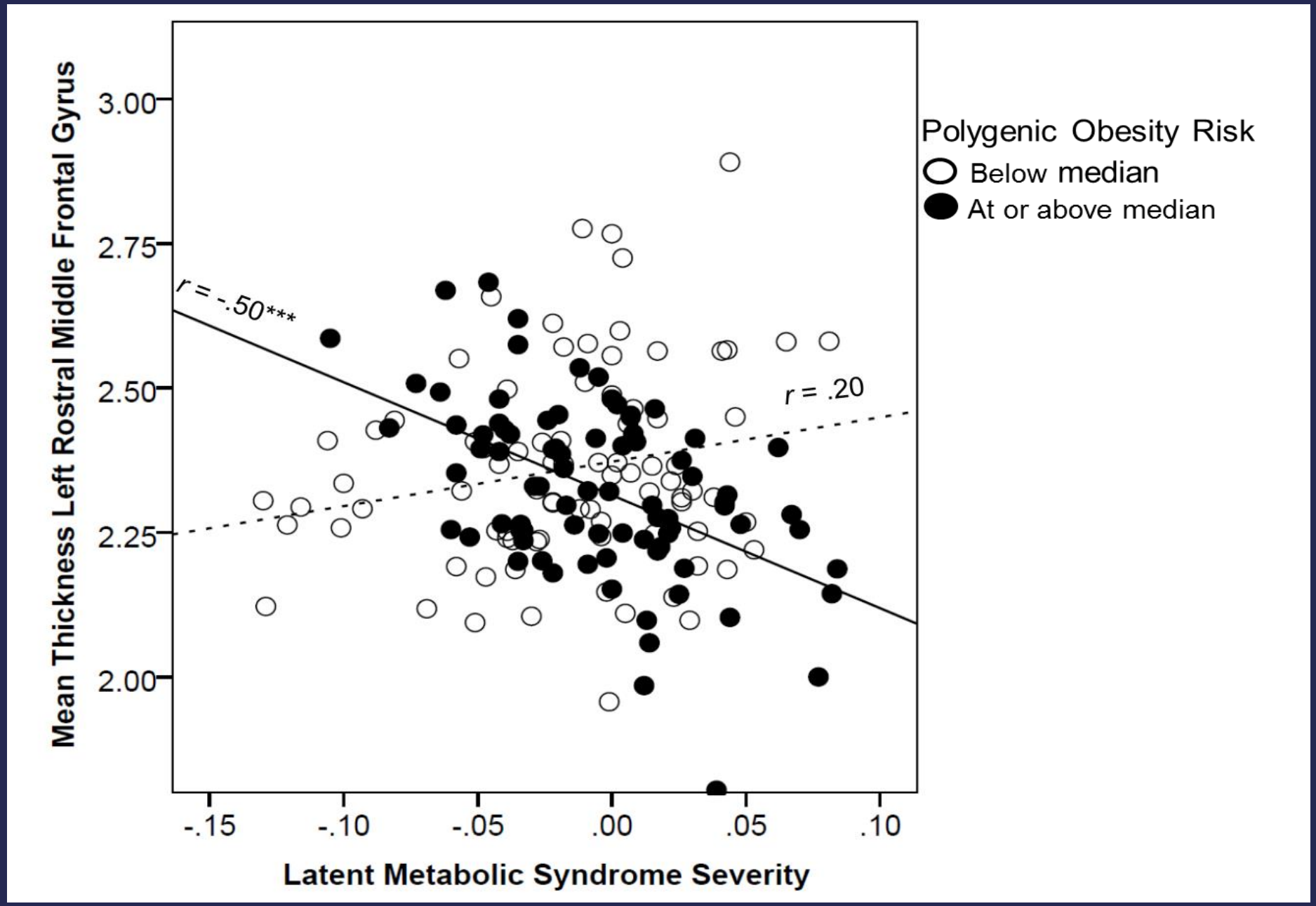
MetS X Obesity Polygenic Risk on Cortical Thickness

- Whole-brain vertex-wise analysis used to evaluate main effects of Obesity PRS on cortical thickness & interactive effects of MetS X Obesity PRS on cortical thickness
  - No sig main effects of Obesity PRS
  - MetS X Obesity PRS yielded effects on left rostral middle frontal gyrus

Obesity PRS X MetS on Left Rostral Middle Frontal Gyrus

Model	Std. β	p	R^2
Main Effects			.038
Age	-.10	.28	
Sex	-.05	.59	
PC1	.01	.87	
PC2	-.05	.56	
Latent Lifetime PTSD Sev	-.004	.96	
MetS Sev	-.08	.44	
Obesity PRS	-.13	.11	
Interaction			.192
MetS X Obesity PRS	-.40	< .001	




Mean Thickness Left Rostral Middle Frontal Gyrus
3.00
2.75
2.50
2.25
2.00
r = -.50***
r = .20
-.15
-.10
-.05
.00
.05
.10
Latent Metabolic Syndrome Severity
Polygenic Obesity Risk
Below median
At or above median

Implications

- PTSD is associated with accelerated aging as reflected in epigenetic, metabolic, health, neural, and cognitive decline
- Substantial pre-mature health decline among young veterans with PTSD is alarming
- Important to identify who is at risk for accelerated aging, identify biological processes at play, develop interventions to stop or reverse accelerated aging
  - DNAm age could be used to identify those at risk for health decline, target interventions, and track response
  - Polygenic risk for obesity could also be evaluated for determining who with PTSD is most at risk for MetS and use this in behavioral and psychopharm treatment recs
  - Screening for MetS features should occur a decade earlier than current recs

Caveats

- Work described is cross-sectional
  - Causal associations not yet evaluated
  - Multivariate stats don’t imply causality
- Small sample size
  - Focused on biomarkers of biology, including neuroimaging parameters
  - Use of single scores to represent genetic and epigenetic variability
  - Use of fit statistics to evaluate overall fit of models relative to data

Future Directions

- Replication in PGC PTSD Epigenetics Workgroup
- R03 from NIA focused on PTSD→DNAm age→MetS
- VA Merit focused on longitudinal associations and early identification of accelerated aging
  - Also collecting RNA, inflammation, other health parameters
- Drill down into DNAm age algorithms to identify gene networks with greatest PTSD-related change over time and those most associated with MetS
- Important to identify moderators of PTSD to age acceleration pathways
  - age, sex, race, genotype
- Explore bio and behavioral mediators of PTSD→DNAm age association
- Identify genetic variants that contribute to pace of cellular aging

http://www.ptsd.va.gov/professional/publications/ptsd-rq.asp

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PTSD and Accelerated Aging

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For hundreds of years, scientists have recognized that the human body is highly sensitive to the external environment. In the mid-1800s, Claude Bernard, who is credited with being among the first to develop and apply scientific methods of experimentation to the study of physiology, suggested that the external environment could alter the "milieu intérieur" (interior environment; Bernard, 1974), the predecessor to the concept of physiological homeostasis. Since that time, a broad research basis has been established focused on understanding how stress, life adversity, and other aspects of the external environment get "under the skin" and lead to poor physical health (e.g., McEwen, 2012). More recently, investigators have suggested that aspects of the intra-individual environment, such as psychiatric symptoms, may impact physiology directly and be as important as the external environment, if not more so, in predicting subsequent health outcomes (e.g., Schnurr & Green, 2004).

This idea has received recent attention in PTSD literature, as there is evidence that PTSD is associated with premature development of physical health problems, ranging from metabolic and cardiovascular diseases, to cognitive decline, to premature death (e.g., Ahmadi et al., 2011; Wolf, Boyin, et al., 2016; Yaffe et al., 2010). Early

They highlighted the PTSD symptoms (e.g., sleep disturbance, emotional arousal) that would be expected to most strongly contribute to cellular aging, and they suggested mechanisms (e.g., epigenetics) and biological systems (e.g., oxidative stress, hypothalamic-pituitary-adrenal axis [HPA] dysfunction) that might contribute to this. Their focus on potential epi/genetic markers of cellular aging was strongly influenced by groundbreaking discoveries in understanding the genetics of aging, as described below.

Up until quite recently, much of the genetic work focused on accelerated aging in PTSD used telomeres as the marker of cellular age. Telomeres are areas of deoxyribonucleic acid (DNA) repeats found at the ends of chromosomes (Blackburn, 2005). As a function of cell division, these repeat DNA sequences become shorter with age, suggesting that telomeres may index accelerated aging when they are shorter than would be expected based on chronological age. Epel and colleagues have developed a large body of groundbreaking research in this area and have shown that many forms of stress, ranging from life adversity to psychological stress to metabolic stress, can influence telomere length (see Epel, 2009 for an

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Thank you!

Questions?