Accelerated Brain and Biological Aging in Serious Mental Illness

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OUTLINE

• Rationale and methodological challenges
• Brain aging in serious mental illness
• Biological aging in serious mental illness
• Future directions
TAKE HOME MESSAGES

• There is premature and accelerated brain aging in serious mental illness
• There is premature and (possibly) accelerated biological aging in serious mental illness
• Mental disorders are whole-body disorders and effective treatments will need to take a systemic approach that considers life-long development
WHY STUDY AGING PROCESS IN SERIOUS MENTAL ILLNESS?

- World’s population is aging & mentally ill are living longer
- Clinical care needs to be responsive to unique issues faced by older mentally ill individuals
- Understanding lifespan trajectories may reveal unique aspects of pathophysiology and suggest ways to slow declines
- Understanding how aging occurs in concert with other brain impairments may also inform our view of aging in general
SCHIZOPHRENIA

- Positive & negative psychotic symptoms and cognitive deficits
- Lifetime prevalence = approx. 1%
- Age of onset 16-25
- Highly disabling
- High annual costs for healthcare and lost productivity
BIPOLAR DISORDER

- Depression, mania / hypomania, psychosis (sometimes), cognitive symptoms
- Lifetime prevalence = nearly 4%
- Median age of onset = 25 years
- Inpatient hospitalization rate = 39.1% (versus 4.5% for other behavioral health care diagnoses)
- Most expensive behavioral health care diagnosis (twice the costs of depression)
ALTERED COURSE OF AGING?

- Premature aging
- Accelerated aging
- Progression

[Diagram showing typical aging, premature aging, and accelerated aging, with functional impairment on the y-axis.]
THE THORNY TRIANGLE

CHRONOLOGICAL AGE

DURATION OF ILLNESS

AGE OF ONSET
DURATION OF ILLNESS / CHRONICITY
CHRONICITY-ASSOCIATED FACTORS
Age at Onset

- Childhood vs typical or “early” vs late
- Qualitative differences?
AGING

Lopez-Otin, Cell, 2013
WHAT EVIDENCE IS NEEDED?

• Premature aging
  • Regardless of duration, patients look older than predicted by chronological age

• Accelerated aging
  • Regardless of duration, patients decline more rapidly than normal

• Progression
  • At any age, those with greater chronicity look worse
  • At any age, accumulation of episodes leads to worsening abnormalities
  • This is true even after controlling for chronicity-associated factors
STUDY DESIGNS

• Young patients vs. old healthy
• Cross-sectional study including range of ages in both patient and comparison group
• Contribution of duration of illness and age of onset
• Longitudinal study
  • How to capture “right” time span
SCHIZOPHRENIA: VOLUMETRIC

- Accelerated ventricular enlargement, more rapid than in healthy individuals, even among chronic patients

Kempton et al, Schizophr Res, 2010
SCHIZOPHRENIA: GRAY MATTER DENSITY

Koutsouleris et al, 2013
SCHIZOPHRENIA: FUNCTIONAL MRI

Eyler et al, AJGP, 2009
Brain may be changing differently with age in those with schizophrenia compared to those without

- Accelerated ventricular volume enlargement
- Premature gray matter density reductions
- Lack of compensatory changes with age in functional responses during learning task
BRAIN AGING IN BIPOLAR DISORDER

- Recently completed R01 from NIMH
- Cross-sectional design
  - Bipolar versus healthy comparison
  - Aged 30-69; matched by 5yr age strata
- Clinical and cognitive assessment
- Biosamples: blood for DNA & saliva for cortisol
- Brain measures
  - Morphometry, diffusion tensor, white matter abnormalities, resting cerebral blood flow (ASL), functional MRI (task-based and resting)
Fear extinction memory performance in a sample of stable, euthymic patients with bipolar disorder

Dean Acheson, Lisa T. Eyler, Jesse Resovsky, Elisa Tsa, Victoria B. Risbrough

Increased Cerebral Blood Flow Associated with Better Response Inhibition in Bipolar Disorder

Sheena I. Dev, Benjamin S. McKenna, Ashley N. Sutherland, David D. Shin, Thomas T. Liu, Christina E. Wierenga, Lisa T. Eyler

Fusing Functional MRI and Diffusion Tensor Imaging Measures of Brain Function and Structure to Predict Working Memory and Processing Speed Performance among Inter-episode Bipolar Patients

Benjamin S. McKenna, Rebecca J. Theilmann, Ashley N. Sutherland, and Lisa T. Eyler

Abnormalities of brain response during encoding into verbal working memory among euthymic patients with bipolar disorder

McKenna BS, Sutherland AN, Legenbaya AP, Eyler LT. Abnormalities of brain response during encoding into verbal working memory among euthymic patients with bipolar disorder.

Benjamin S. McKenna, Ashley N. Sutherland, Anna P. Legenbaya, and Lisa T. Eyler
ACCELERATED WHITE MATTER AND COGNITIVE AGING

Dev et al, 2017
MULTI-MODAL BRAIN AGE ANALYSIS

- $N = 126$ participants between ages 30-80
  - 47 euthymic outpatients with bipolar I disorder
  - 79 healthy comparison (HC) subjects; subset of 52 with age and education comparable to BD
BRAIN MEASURES

- **Volume, surface area, and thickness** within Freesurfer subcortical and cortical parcels
- **Mean blood oxygenation level dependent (BOLD) response** to load in clusters of group activation during 2 working memory tasks
- **Within-network correlations of resting BOLD** between task negative (default mode) and positive nodes
- **Deep and periventricular volume of white matter hyperintensities**
- **Mean fractional anisotropy within tracts** from Hopkins atlas and tract-based spatial statistics based on diffusion tensor images
- **Mean cerebral blood flow** within Freesurfer subcortical and cortical parcels
BRAIN AGE ANALYSIS METHOD

- Partial least squares regression in full HC sample to predict chronological age from all brain measures
- Resulting equation used to calculate brain age for HC and BD subjects
- Brain Age minus Age = Brain Age Discrepancy
- Compared Brain Age Discrepancy between BD and matched HC; correlated with clinical features in BD
BRAIN AGE PREDICTED ± 1 YEAR IN HEALTHY GROUP
BIPOLAR DISORDER: MULTIMODAL BRAIN AGE 4.7 YEARS OLDER

$p < 0.003$
BRAIN AGE CORRELATES

• In BD group, brain age discrepancy was largest among:
  • Younger individuals (r = -.47, p = 0.002)
  • Men (11±10.1 years vs. 2.6±10.6, t (45) = -2.4, p = 0.02)
  • Individuals with lower premorbid IQ (r = -0.38, p = 0.01)
  • Individuals with more manic episodes relative to their age (partial r = 0.34, p = 0.04)
BIPOLAR BRAIN AGING: SUMMARY

- Premature aging for white matter hyperintensities
- Possible accelerated aging for uncinate fasciculus white matter microstructure
- Multi-modal brain age 4.7 years older than actual age
- Possible progression due to manic episodes?

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Brain Age Discrepancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koutseleris, 2013</td>
<td>Major depression</td>
<td>4 years</td>
</tr>
<tr>
<td>Koutseleris, 2013</td>
<td>Schizophrenia</td>
<td>5.5 years</td>
</tr>
<tr>
<td>Cole, 2015</td>
<td>Traumatic Brain Injury</td>
<td>6 years (white matter)</td>
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<tr>
<td>Franke, 2010</td>
<td>Alzheimer’s</td>
<td>10 years</td>
</tr>
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ALTERED COURSE OF AGING?

- Premature aging
- Accelerated aging
- Progression
ACCELERATED PHYSICAL / BIOLOGICAL AGING

- High physical morbidity from usual natural causes of aging-related diseases (cardiac, metabolic)
- High mortality and shortened life span
- Reports of worse levels of aging-associated (systemic) biomarkers from cross-sectional studies
  - Inflammation, in particular, linked to body and brain aging in those without mental illness
“Did Carrie Fisher's Bipolar Disorder Contribute to Her Death?”

-- Scientific American
12/31/2016
SCHIZOPHRENIA ACCELERATED AGING STUDY (D. JESTE, PI)

• 140 subjects with SZ & 120 healthy comparison subjects (HCs) aged 26-65 years (mean age 48), using a Multi-cohort (Accelerated) Longitudinal Design

• 4 blood-based systemic biomarkers: 1) Homeostatic Model Assessment of Insulin Resistance or HOMA-IR, 2) high sensitivity C-Reactive Protein or hs-CRP, 3) F2-isoprostanes, and 4) telomere length in peripheral blood mononuclear cells.

• Also examined a number of chemokines, cytokines (IL-6, TNF-α, IFN-γ), and vascular endothelial markers (VEGF, ICAM1, VCAM1)

• Clinical assessment every year, & biomarker data alternate years
## 4 MAIN BIOMARKERS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Healthy Controls (n=133)</th>
<th>Schizophrenia (n=139)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOMA-IR***</td>
<td>1.8 (1.6)</td>
<td>3.6 (5.1)</td>
</tr>
<tr>
<td>F2-Isoprostanes**</td>
<td>0.03 (0.02)</td>
<td>0.04 (0.02)</td>
</tr>
<tr>
<td>hs-CRP***</td>
<td>2.1 (3.4)</td>
<td>5.1 (8.7)</td>
</tr>
<tr>
<td>Telomere length (Relative)</td>
<td>5,668.2 (500.1)</td>
<td>5,613.1 (394.4)</td>
</tr>
</tbody>
</table>

**p<.01; ***p<.001

Lee et al, in prep; Joseph et al, 2015; Lee et al, 2016
## CHEMOKINES

<table>
<thead>
<tr>
<th>Variable</th>
<th>Healthy Controls (n=113)</th>
<th>Schizophrenia (n=134)</th>
</tr>
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<tbody>
<tr>
<td>MCP-1***</td>
<td>89.2 (56.3)</td>
<td>97.8 (36.8)</td>
</tr>
<tr>
<td>MIP-1β**</td>
<td>60.4 (27.2)</td>
<td>72.2 (35.9)</td>
</tr>
<tr>
<td>Eotaxin-1***</td>
<td>114.9 (53.7)</td>
<td>151.6 (99.4)</td>
</tr>
<tr>
<td>TARC*</td>
<td>62.4 (41.3)</td>
<td>83.5 (65.8)</td>
</tr>
<tr>
<td>MDC**</td>
<td>760.7 (356.1)</td>
<td>933.1 (456.7)</td>
</tr>
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* *p<.05; ** p<.01; *** p<.001

Hong et al, 2017
### CYTOKINES

<table>
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<th>Variable</th>
<th>Healthy Controls (n=95)</th>
<th>Schizophrenia (n=95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-α***</td>
<td>2.51 (0.8)</td>
<td>3.06 (1.1)</td>
</tr>
<tr>
<td>IL-6***</td>
<td>0.94 (1.6)</td>
<td>1.16 (1.0)</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>8.2 (13.6)</td>
<td>9.0 (17.1)</td>
</tr>
</tbody>
</table>

- Depression symptoms associated with TNF-α and IL-6 levels
- Physical comorbidity greater in those with higher IL-6 levels
VASCULAR ENDOTHELIAL MARKERS

VEI

VEI: non-smokers

Nguyen et al, under review
SYSTEMIC ACCELERATED AGING?

- Systematic review of 42 published articles
  - Systemic markers (blood or tissue)
  - Examined age relationships in SZ and HC
- 75% showed evidence for premature aging
  - “Older” biomarkers in SZ vs HC
- 26% showed differential age relationships
  - Synaptic and gene expression markers most likely to show steeper negative slope in SZ
- Inflammation and telomere length related to duration of illness

Nguyen et al, under review
PLANNED ANALYSES

• Cohort effects at baseline (younger patients less healthy than older) obscuring possible signs of differential aging
• Longitudinal analyses needed
  • Funded for another 5 years
  • Multi-year trajectories for main biomarkers
  • Addition of more sophisticated inflammatory markers
Bipolar Disorder: Role of Inflammation and the Development of Disease Biomarkers

Ather Muneer

Cytokines in Bipolar Disorder: Paving the Way for Neuroprogression

Izabela Guimarães Barbosa,¹ Moisés Evandro Bauer,² Rodrigo Machado-Vieira,³,⁴ and Antonio Lucio Teixeira¹,⁵

Inflammation as a neurobiological substrate of cognitive impairment in bipolar disorder: Evidence, pathophysiology and treatment implications

Joshua D. Rosenblat⁴,¹, Elisa Brietzke⁴,¹, Rodrigo B. Mansur⁴,¹, Nadia A. Maruschak⁴,¹, Yena Lee⁴,¹, Roger S. McIntyre⁴,¹,*
**DYNAMIC INFLAMMATORY AND MOOD PREDICTORS OF COGNITIVE AGING IN BIPOLAR DISORDER**

- Ongoing R01 from NIMH
- “Burst” accelerated longitudinal design

![Timeline Diagram](image)

- 144 bipolar I and 115 non-bipolar comparison participants
- Baseline ages 35-60
- Ecological momentary assessment of mood, stress, coping, sleep, medication adherence, cognitive complaints, drug/alcohol use
- Actigraphy watches for physical activity and sleep
- Biosamples: blood for inflammatory markers and DNA

UC San Diego
School of Medicine
PRELIMINARY RESULTS

• BD (n=17) and HC (n=40)
• CRP, TNF-$\alpha$, and IL-6 higher in BD than HC
• Levels of CRP were more variable across three visits in BD than HC
• Correlates of mean levels
  • ↑ depressive symptoms = ↑ CRP and IL-6
  • ↑ mania symptoms = ↑ IL-6
• Correlates of intra-individual variability
  • ↑ baseline systolic BP = ↑ CRP and IL-6 variability
GAPS IN OUR KNOWLEDGE

• Long-term, longitudinal trajectory of symptoms, cognition, and brain in individual patients
• Understanding individual differences in trajectories
• Determining best prognostic markers
• Discovering modifiable risk factors to prevent or slow declines in those vulnerable to declines
INFLAMMATION AND THE BRAIN

- N=14 older adults (mean age = 78)
- BOLD activation during a working memory task
- Blood-based markers of inflammation (CRP and IL-6)

Dev et al, 2017
FUTURE DIRECTIONS

• Association of inflammatory markers with physical activity levels (Dev)

• Relation of blood-based biomarkers of aging and inflammation to brain measures (Nguyen)

• Longitudinal imaging studies, including measures of neuroinflammation (Powell, Bussell)

• Understanding role of ethnicity in risk for accelerated biological and brain aging (Lee, Carrasco)

• Use of proteomics and transcriptomics to characterize the function of “neurons in a dish” from younger and older patients with schizophrenia (Lietz, Reed)
TREATMENT IMPLICATIONS

- Lifestyle interventions (diet, exercise, smoking cessation)
  - Good for the body and brain
- Earlier diagnosis and treatment of symptoms that may contribute to declines
- Anti-inflammatory treatments?
TAKE HOME MESSAGES

• There is premature and accelerated brain aging in serious mental illness

• There is premature and (possibly) accelerated biological aging in serious mental illness

• Mental disorders are whole-body disorders and effective treatments will need to take a systemic approach that considers life-long development
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