Diversity in cognitive aging and risk of Alzheimer’s Disease

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Study Participants of:
Chicago Health and Aging Project
Minority Aging Research Study
Clinical Core
Rush Memory and Aging Project
Religious Orders Study
Objectives

- Review existing epidemiologic evidence on disparities in Alzheimer’s dementia among older African Americans
- Identify genetic and environmental risk factors for cognitive impairment and cognitive decline among older African Americans
- Explore patterns of AD pathology among African Americans and Whites
U.S. is becoming increasingly diverse
Alzheimer’s Association estimates that African Americans are ~ 2x more likely than Whites to have Alzheimer’s disease

40% less likely to get treatment
African Americans are about twice as likely to have AD.
Age-standardized dementia incidence rates by race/ethnicity, 2000-2013

Mayeda et al., 2016
Well-documented that African Americans perform more poorly than Whites on cognitive function tests.
Cognitive tests used to make diagnosis are influenced by many factors.
Longitudinal design may be a better way to examine race differences in cognitive aging

• Reliable estimate of change in cognitive function
• Control for baseline level of function
• Can examine level and slope separately
• Each person serves as own control
Prevention is an important action area

- Identify risk factors (genetic/environmental)
- Determine biologic pathways linking risk factors to disease
- Develop strategies to prevent AD and reduce disparities
  - Modify lifestyle behaviors
  - Identify drugable targets and develop effective therapeutics
Rush Cohort Studies

- Chicago Health and Aging Project (CHAP)
- Minority Aging Research Study (MARS)
- Rush Clinical Core
- Rush Memory and Aging Project (MAP)
- Religious Orders Study (ROS)
CHAP Design

- Population-based
- Complete census of all households
- All residents aged 65+ invited to participate
- Of 7,813 eligible, 6,158 enrolled
- ~60% African American
Data Collection

- In-person, in-home interviews
- 3-year cycles, starting in 1993
- In 2000 (3\textsuperscript{rd} wave), began recruiting newly aged persons
- Original + successive cohorts, N=10,800
Minority Aging Research Study and Rush Clinical Core:

- Two cohort studies of aging and AD among African Americans
- >1,000 older persons, >65 years, without [known] dementia recruited from the community
- All agreed to annual detailed clinical evaluation with risk factors assessment and blood donation
- All visits conducted as face-to-face evaluations in the home
- Organ donation is encouraged but not required

PI: Barnes, LL
“In the heart of the community, ever seeking to win the community’s heart”
Religious Orders Study and Rush Memory and Aging Project:

- Two cohort studies of aging and AD ongoing for 20+ years
- >3,000 older persons without [known] dementia from across the USA, ~91% White
- All agreed to annual detailed clinical evaluation with risk factors assessment and blood donation
- All agreed to organ donation at death
- > 1,200 autopsies
- Significant overlap in risk factors with MARS/Clinical Core and all have harmonized cognitive battery

PI: Bennett, DA
Cognitive Function

Composite of 19 performance-based tests

**Episodic memory** (immediate and delayed story recall & word list recall/recognition)

**Semantic memory** (naming pictures, fluency, reading)

**Working memory** (digits forward, backward, & ordering)

**Perceptual speed** (digit symbol, number comparison)

**Executive function** (Stroop reading, Stroop color)

**Visuospatial ability** (line orientation, progressive matrices)
5 Rush Cohort Studies of cognitive aging

**CHAP**
- Large, population-based
- Living in contiguous neighborhoods
- 60% African American
- Range of SES across both groups
- Brief 4-test cognitive battery

**MARS/Clincore + MAP/ROS**
- Volunteer
- Recruited from community
- All enrolled without dementia
- Followed annually
- Involve organ donation (required for Whites)
- 19-test cognitive battery
Significant heterogeneity exists in cognitive decline and much is driven by persons with AD.
No race differences in rates of cognitive decline in older African Americans and Whites (CHAP)

Weuve et al., 2018
Similar results in community studies: No race difference in decline

Wilson et al., 2015
Also no racial differences when examine non-linear change

*From mixed effects change point models adjusted for age & education

Wilson et al., 2017
African Americans with AD decline at 25% slower rate than Whites with AD

Dotted line: African American  
Solid line: White

Barnes et al., 2005
Cognitive aging summary

African Americans perform worse, on average, on tests of cognition in cross-sectional analyses.

No evidence for faster rates of decline in longitudinal analyses.
Risk Factors for Cognitive Aging

• Factors that predict decline
• Role of race or factors related to race
Established Risk Factors

**Increase Risk**
- Race
- Age
- Family History
- Genetic mutations
  - Amyloid precursor protein (APP, 21q)
  - Presenilin 1 (PS1, 14q)
  - Presenilin 2 (PS2, 1q)
- Genetic polymorphisms
  - Apolipoprotein E ε4 allele

**Decrease Risk**
- Education
- Genetic polymorphisms
  - Apolipoprotein E ε2 allele
Apolipoprotein E ε4 allele

• APOE ε4 – most robust genetic risk factor for AD in Whites
• Frequency of the ε4 allele higher in African Americans, but effect is weaker
• Most studies only examined brief screening tools
• What is the effect of ε4 on change in different cognitive domains?
APOE-ε4 is related to faster decline in episodic memory in both African Americans & Whites

But no effect of ε4 in other domains for African Americans

Barnes et al., 2013
Apolipoprotein E ε4 allele

• Another possibility for discrepant results with ε4 is the race specific variation of haplotypes across APOE and neighboring genes

• Pattern of linkage between APOE and TOMM40 differs between African Americans and Whites
  – White - ε4 almost perfectly linked with ‘523-L allele
  – AA - ε4 is linked to ‘523-S in addition to ‘523-L

• Could this explain the weaker effect of ε4 in African Americans?
Different cluster of haplotypes (TOMM40) for ε4
APOE ε4-TOMM40 ‘523 and risk of AD in Blacks & Whites

Yu et al., 2017
How do race-relevant factors influence cognition and cognitive decline?

- Early life residence
- School segregation
- Perceived stress
- Discrimination
- Neighborhood conditions
- Caregiving stress
- Financial burden
- Racial identity
- John Henryism
- Spirituality/religiosity
- Occupational complexity
African Americans from the South perform worse on cognitive function tests than those from the North

Early life residence and cognition

Lamar et al., 2019
Early life residence and cognition

African Americans born in the South perform worse on cognitive function tests than those born in the North.
African Americans from the South who attended a desegregated school perform the worst

Lamar et al., 2019
Perceived Stress is related to faster decline

degree to which a person finds their lives unpredictable, uncontrollable, and overloading

Episodic memory
Visuospatial Ability

Turner et al., 2017
Self-reported Experiences of Discrimination

- Discrimination is an important psychosocial stressor with links to adverse health outcomes
- Some, but not all studies have found it partially explains disparities in health
Perceived discrimination is associated with worse episodic memory & perceptual speed

<table>
<thead>
<tr>
<th>Variables</th>
<th>Global cognition</th>
<th>Episodic memory</th>
<th>Perceptual speed</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.02 (.004)**</td>
<td>-0.03 (.004)**</td>
<td>-0.04 (.005)**</td>
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<tr>
<td>Sex</td>
<td>-0.08 (.052)</td>
<td>-0.17 (.064)*</td>
<td>-0.17 (.076)*</td>
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<tr>
<td>Education</td>
<td>0.07 (.007)**</td>
<td>0.04 (.008)**</td>
<td>0.09 (.010)**</td>
</tr>
<tr>
<td>Discrimination</td>
<td>-0.02 (.010)*</td>
<td>-0.03 (.013)*</td>
<td>-0.04 (.015)*</td>
</tr>
</tbody>
</table>

**=p<.01; *=p<.05

Much of the association explained by depressive symptoms

Barnes et al., 2013
Self-reported experiences of everyday discrimination are associated with elevated C-reactive protein levels in older African-American adults

Tené T. Lewis\textsuperscript{a,*}, Allison E. Aiello\textsuperscript{b}, Sue Leurgans\textsuperscript{c,d,e}, Jeremiah Kelly\textsuperscript{c,d}, Lisa L. Barnes\textsuperscript{c,d,f}

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Lewis et al., 2010
Greater perceived discrimination among African Americans is associated with (1) less functional connectivity of the left insula (involved in trust perception) to the dorsolateral prefrontal cortex, and (2) greater functional connectivity of the left insula to the visual cortex.
Risk factor summary

There may be genetic differences by race on the effect of AD that is driven by variation in pattern of linkage with neighboring genes.

But there also appear to be culturally-relevant factors that may help us understand within-race heterogeneity; these factors affect cognitive test performance and associate with blood & brain markers.
Race and pathology
By Age 85:

- Alzheimer’s disease changes present in nearly every brain
  - About 80% have amyloid
  - Nearly all have tangles
  - More than 60% meet the NIA-Reagan threshold for the pathologic diagnosis of AD
  - More than half have moderate-severe amyloid angiopathy

- Cerebrovascular disease present in more than half of brains
  - More than a third have macroscopic infarcts
  - More than a third have microscopic infarcts
  - Nearly 20% have both

- Parkinson’s disease changes present in 40% of brains
  - More than a third have nigral degeneration
  - Nearly 20% have Lewy bodies
  - More than 10% with both

- Up to 40% of brains are positive for TDP-43
Mixed brain pathologies in dementia

Limited data on neuropathology in African Americans

- Is pathology the missing link in understanding the disparities in AD?
  - More vascular disease among African Americans?
African Americans and Whites with AD dementia

- African Americans more likely to have mixed pathology as cause of dementia.
- Mixed pathology includes AD & LB, not vascular as hypothesized.

Figure: Racial differences in mixed pathology

Pie chart shows proportions of individual and mixed pathologies in black and white decedents with Alzheimer disease (AD) dementia. INF = infarcts; LB = Lewy bodies.

Barnes et al., 2015, Neurology
Conclusions

• Increased risk of AD among African Americans seems to be due to persistent racial differences in cognitive level

• Culturally-relevant variables need to be incorporated to understand risk and promotors of healthy aging
  – Risk markers reflecting stressful social conditions or disadvantage were associated with cognition; suggest modifying or intervening on the ways that people experience stress, may be targets to promote resilience

• In persons with dementia, there appear to be differences in the patterns/frequencies of pathology that cause dementia
  – Possibly due to selection bias of who shows up to a memory clinic
  – Future studies needed in community-based cohorts of persons without dementia
Future Directions

• Neuroimaging – the neurobiologic substrates of cognitive aging in vivo

• Decision making – determinants and adverse consequences of racial differences in decision making

• Racial differences in pathology from participants in community-based studies
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