30th Annual Southern California Alzheimer’s Disease Research Conference to be held on Friday, October 25, 2019

30 Years of Discovery: Hope on the Horizon

GIFTED BRAINS YIELD PRICELESS GAINS

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The Deborah R. And Edgar D. Jannotta Presidential Professor of Pathology (Neuropathology) and Neurological Sciences

Associate Director, Rush Alzheimer's Disease Center, Rush University Medical Center
What are we learning from the precious gift of brain donation from older persons?

- Alzheimer’s disease pathology is often mixed with other pathologies (mixed pathology)

- Risk factors may work through increasing/decreasing pathology.

- Persons without cognitive impairment may have a lot of “subclinical” pathology

- There is pathologically unexplained cognitive change and risk factors
Auguste D & Alois Alzheimer

- First patient described - 1907
  - 51 year old woman
  - Memory impairment
  - Hallucinations, delusions, paranoia
  - Agitation
  - Disorientation

- Progression over 5 years
  - At end - fetal position, incontinent, unresponsive
Autopsy brain examination

- Grossly atrophic
- Microscopic exam:
  - Neuronal loss
  - Neuritic plaques
  - Neurofibrillar tangles
The Religious Orders Study

Began in 1993
- Older nuns, priests, and brothers without known dementia from across the U.S.
- All agreed to annual cognitive testing
- All agreed to brain donation at the time of death

The Rush Memory and Aging Project

Began in 1997
- Study with similar methods but lay population more reflective of general population - from about 40 retirement communities and senior housing
- All agreed to annual cognitive/motor testing, blood draws
- All agreed to donate brain, spinal cord, muscle, nerve at the time of death
- F/U rates over 90% Autopsy Rates 80%

Both studies on going for 20+ years • >3,000 older persons enrolled without [known] dementia from across the USA, over 1500 autopsies
Religious Orders Study Sites
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The pathologies of the aging brain

• **NEURODEGENERATIVE**
  • Alzheimer’s disease (plaques/tangle)
  • Lewy body disease
• TDP-43 pathology
• Hippocampal sclerosis

• **VASCULAR**
  • Macroinfarcts (strokes)
• Microinfarcts
• CAA
• Atherosclerosis
• Arteriolosclerosis
Mixed brain pathologies common in MCI and probable AD

Figure 1. Probability of dementia by Alzheimer disease pathology showing additive effects of macroscopic infarcts and microinfarcts.

Relation of Cerebral Vessel Disease to Alzheimer’s Disease
Dementia and Cognitive Function in Older Persons: A Cross-
sectional Study

Zoe Arvanitakis, MD1,2, Ana W. Capuano, PhD1,2, Sue E. Leurgans, PhD1,2, David A. Bonnett, MD1,2, and Julio A. Schneider, MD1,2,3

AD pathology – global score

AD dementia

No infarct or vessel pathology
Gross infarcts
Gross infarcts and microinfarcts
Gross infarcts, microinfarcts, and atherosclerosis
Gross infarcts, microinfarcts, atherosclerosis, and arteriolosclerosis (all infarcts and vessel pathologies)

0
0.2
0.4
0.6
0.8
1.0

Probability of Alzheimer’s disease dementia
Lewy Bodies - Pathology first described in Parkinson’s disease

Lewy body Dementia

Schneider JA et al. Brain 2012;135:3005-3014
TDP-43 new “kid on the block” in aging and AD

ubiquinated protein in FTLD-U and ALS; 414 AA nuclear DNA/RNA binding protein; regulates gene expression, splicing/stability of RNA transcripts

• Related to amnestic dementia, mimics Alzheimer’s Dementia
• Commonly co-occurs with AD and lowers memory
• Strongly related to cognitive decline – especially memory
• Accumulation is associated with hippocampal degeneration and ultimately hippocampal sclerosis
REVIEW

Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report

Peter T. Nelson,1,2 Dennis W. Dickson,2,3 John Q. Trojanowski,1,2 Clifford R. Jack Jr.,4 Patricia A. Boyle,5 Konstantinos Arfanakis,5,6 Rosa Rademakers,2,4 Irina Alafuzoff,7 Johannes Attems,2 Carol Brayne,7 Ian T.S. Coyle-Gilchrist,8 Helena C. Chui,1,9 David W. Farlow,1 Margaret E. Flanagan,11,12 Glenda Halliday,12 Suvi R.K. Hokkanen,9 Sally Hunter,9 Gregory A. Jicha,1 Yuri Ko Katsuragawa,1 Claudia H. Kwas,10 C. Dirk Keene,14 Gabor G. Kovacs,14 Walter A. Kukull,15 Allan I. Levey,16 Naznin Makkinejad,6 Thomas J. Montine,17 Shigeo Murayama,18 Melissa E. Murray,2 Sukriti Nag,3 Robert A. Risman,19 William W. Seeley,20 Reisa A. Sperling,21 Charles L. White III,22 Lei Yu1 and Julie A. Schneider3

Box 1 LATE and LATE-NC summary points

- LATE-NC features
  - A sampling and staging system for routine autopsy diagnosis is proposed to characterize the anatomical distribution of TDP-43 proteinopathy
    - Stage 1: amygdala only
    - Stage 2: + hippocampus
    - Stage 3: + middle frontal gyrus
  - Hippocampal sclerosis pathology may be observed (and should be reported), but is neither necessary nor sufficient for diagnosis of LATE-NC
- LATE-NC is present in >20% (up to 50%) of individuals past age 80 years according to large community-based autopsy series
- LATE is associated with substantial disease-specific cognitive impairment, usually an amnestic dementia syndrome (‘dementia of the Alzheimer’s type’)
- The overall public health impact of LATE is on the same order of magnitude as Alzheimer’s disease neuropathological changes; the diseases are often comorbid, but which pathology is more severe varies greatly between individuals
- Genetic risk factors for LATE have some overlap with FTLD-TDP and with Alzheimer’s disease
- There is no molecule-specific biomarker for LATE. This is an important area of need for use in clinical trials (including as a potential exclusion criterion for Alzheimer’s disease clinical trials) and longitudinal studies of the clinical and pathological progression of LATE

~ 900 cases

N= 946 ROS/MAP
n=398 AD dementia
n= 548 no AD dementia

496 (52%) with TDP

% of mixed pathologies in clinical AD increased 60% to over 80% when considering TDP -43.
Mixed pathologies published in multiple cohorts/populations/groups

Deenerative and vascular lesions of the brain have synergistic effects in dementia of the elderly.

March 12, 1997
Brain Infarction and the Clinical Course of Alzheimer Disease: The Nun Study
David A. Snowdon, PhD; Lydia H. Greiner

The effects of additional pathology on the cognitive deficit in Alzheimer disease.
Nagy Z, Esiri MM, Jobst KA, Morris JH, King EM, McDonald B, Joachim C, Litchfield S, Bamelman L, Smith AD.

TDP-43 pathology in Alzheimer's disease, dementia with Lewy bodies and ageing.
McAleese KE, Walker L, Erksine D, Thomas AJ, McKeith IG, Attems J.

Published: 20 January 2001
## UPDATE ON MIXED PATHOLOGIES INCLUDING NEW FINDINGS

<table>
<thead>
<tr>
<th></th>
<th>NCI</th>
<th>MCI</th>
<th>Probable AD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AD path diagnosis</strong></td>
<td>42.5% (153/360)</td>
<td>61.2% (166/271)</td>
<td>85% (380/447)</td>
</tr>
<tr>
<td><strong>Pure AD path dx</strong></td>
<td>8.3%</td>
<td>7.4%</td>
<td>3.1%</td>
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<tr>
<td><strong>Mixed AD path + other Degenerative + vascular</strong></td>
<td>11.67%</td>
<td>23.62%</td>
<td>47.0%</td>
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</tbody>
</table>

Kapasi A et al. Acta Neuropathologica 2017
• AD most common pathology (65%)

• But AD occurred alone < 9%

• AD, TDP-43, and CAA most commonly co-morbid but depending on specific combination present in between 22 and 41 persons

• More than 230 combinations of pathology –

• most combinations in less than 20 persons
Top 10 most specific combinations of pathology

1. AD only; n=64; 5.9%

2. none of the 9; n=62; 5.8%

3. AD and CAA, n=41; 3.8%

4. AD + CAA + TDP, n=26; 2.4%

5. Gross infarcts, n=24; 2.2%

6. Atherosclerosis, n=22, 2.0%

7. AD + TDP, n= 18, 1.7%

8. TDP43, n= 17; 1.6%

9. AD + atherosclerosis, n=17; 1.6%

10. Microinfarcts, n=16; 1.5%
How much dementia could be averted by eliminating specific groups of pathology?

(Using logistic regression models that include age and pathologies with dementia as outcome)

Pathologic AD - fraction averted 52%*

Lewy bodies, HS, and TDP........36.8%

Infarcts, CAA, athero-, arteriolosclerosis......46.8%

* Cohort specific estimates/ not accounting for other pathologies

** Note numbers do not add up to 100 since there is inter-relationships between pathologies.
Pathology and dementia in the oldest old (age 90+ vs. <90)

James BD et al., JAMA. 2012 May 2;307(17):1798-800.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=804)</th>
<th>Age 65-89 (n=503)</th>
<th>Age 90+ (n=301)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at death, yrs(SD)</td>
<td>87.7 (6.7)</td>
<td>83.8 (4.8)</td>
<td>94.3 (3.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dementia(^a), no. (%)</td>
<td>304 (37.8%)</td>
<td>143 (28.4%)</td>
<td>161 (53.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AD(^c)</td>
<td>493 (61.3%)</td>
<td>279 (55.5%)</td>
<td>214 (71.1%)</td>
<td>&lt;0.001</td>
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<tr>
<td>Infarcts(^d)</td>
<td>272 (33.8%)</td>
<td>147 (29.2%)</td>
<td>125 (41.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Single path</td>
<td>374 (46.5%)</td>
<td>238 (47.3%)</td>
<td>136 (45.2%)</td>
<td>0.56</td>
</tr>
<tr>
<td>Mixed path</td>
<td>225 (28.0%)</td>
<td>113 (22.5%)</td>
<td>112 (37.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AD + LB</td>
<td>41 (5.1%)</td>
<td>25 (5.0%)</td>
<td>16 (5.3%)</td>
<td>0.83</td>
</tr>
<tr>
<td>AD + Infarcts</td>
<td>162 (20.2%)</td>
<td>79 (15.7%)</td>
<td>83 (27.6%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
What are we learning from the precious gift of brain donation from older persons?

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Multiple Potential Pathways to Dementia

*Lifestyle Factors*
- physical activity
- diet
- drug/alcohol abuse

*Environmental Factors*
- education
- head trauma
- toxins/other

*Psychosocial Factors*
- depression/anxiety
- Aging

*Genetic Factors*
- Sex F>M

*Other Medical Risks*
- hypertension
- obesity
- stroke
- heart disease
- diabetes
- metabolic
- inflammation
- certain infectious diseases
- certain medications

*Health Disparities Factors*

*Misfolded proteins*  
- amyloid
- tau
- alpha synuclein
- TDP-43

*Vascular Disorders*  
- infarct (stroke)
- white matter disease
- blood vessel disease

*Other Disorders*  

*BRAIN CHANGES*

*Cognitive Impairment Including Dementia*
- Alzheimer’s Dementia
- Lewy Body Dementias
- Vascular Dementias
- Frontotemporal Dementias
- Limbic Predominant TDP
- Mixed Dementias
- Other Cognitive Impairment
- Other Dementias

Concept by:
Julie A. Schneider, MD, MS, Rush University &
Roderick A. Corriveau, PhD, NINDS
Elevated systolic blood pressure related to infarcts and tangles
Vitamin E in the brain related to more vs. less amyloid depending on the type of tocopherol!
What are we learning from the precious gift of brain donation from older persons?

• Alzheimer’s pathology often mixed with other pathologies (mixed pathology)

• Risk factors and genetics may work through increasing pathology, resilience or unknown mechanisms.

• Persons without cognitive impairment may have a lot of subclinical pathology (resilience)

• There is a lot we still don’t know about the brain changes of cognitive decline in aging.
Pathology in those without MCI or dementia

Pathology without cognitive impairment...

Lesser amounts of pathology

? Better repair mechanisms

? Less or “better” inflammation

? Compensation via other pathways
Memory complaints are related to Alzheimer disease pathology in older persons

L.L. Barnes, PhD, J.A. Schneider, MD, P.A. Boyle, PhD, J.L. Bienias, ScD, and D.A. Bennett, MD
Rush Alzheimer’s Disease Center (L.L.B., J.A.S., P.A.B., D.A.B.) and Rush Institute for Healthy Aging (J.L.B.) and Departments of Neurological Sciences (L.L.B., J.A.S., D.A.B.), Internal Medicine (J.L.B.), and Behavioral Sciences (L.L.B., P.A.B.), Rush University Medical Center, Chicago, IL.

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Memory Complaints, Dementia, and Neuropathology in Older Blacks and Whites

Zoe Arvanitakis, MD, MSa,b, Sue E. Leurgans, PhDa,b, Debra A. Fleischman, PhDab,c, Julie A. Schneider, MD, MSa,b,d, Kumar B. Rajan, PhDe, Jeremy J. Pruzin, MDab, Raj C. Shah, MDab, Denis A. Evans, MDc, Lisa L. Barnes, PhDbabc, and David A. Bennett, MDab


Olfactory impairment in presymptomatic Alzheimer’s disease.

Wilson RS1, Arnold SE, Schneider JA, Boyle PA, Buchman AS, Bennett DA.
Correlates of Susceptibility to Scams in Older Adults Without Dementia

Bryan D. James, PhD, Assistant professor,1,2 Patricia A. Boyle, PhD, Associate professor,1,3 and David A. Bennett, MD, Professor and Director1,4

Scam Awareness Related to Incident Alzheimer Dementia and Mild Cognitive Impairment: A Prospective Cohort Study.

Boyle PA1, Yu L1, Schneider JA1, Wilson RS1, Bennett DA1.
Senior's weakness for scams may be warning sign of dementia

by Lauran Neergaard

In this May 19, 2015, file photo, a doctor points to PET scan results that are part of a study of…

Does an older friend or relative have a hard time hanging up on telemarketers? Or get excited about a “You’ve won a prize” voicemail? New research suggests seniors who aren’t on guard against scams also might be at risk for eventually developing Alzheimer’s disease.
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• Persons without cognitive impairment may have a lot of subclinical pathology (resilience)

• There is a lot we still don’t know about the brain changes of cognitive decline in aging.
Much of late life cognitive decline is not due to common neurodegenerative pathologies

Patricia A. Boyle, PhD\textsuperscript{1,2}, Robert S. Wilson, PhD\textsuperscript{1,2,3}, Lei Yu, PhD\textsuperscript{1,3}, Alasdair M Barr, PhD\textsuperscript{4}, William G. Honer, M.D.\textsuperscript{5}, Julie A. Schneider, MD\textsuperscript{1,3,6} and David A. Bennett, MD\textsuperscript{1,3}

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Boyle et al.

Figure 3.
Variation in cognitive decline explained by the pathologic indices (grey) and the residual, unexplained variation in cognitive decline (white) derived from fully adjusted models.
Late-Life Depression is Not Associated with Dementia Related Pathology

Robert S. Wilson, PhD, Patricia A. Boyle, PhD, Ana W. Capuano, PhD, Raj C. Shah, MD, George M. Hoganson, MD, Sukriti Nag, MD, PhD, and David A. Bennett, MD
Rush University Medical Center


Brain IGFBP-5 modifies the relation of depressive symptoms to decline in cognition in older persons.


Author information

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Vulnerability to Stress, Anxiety, and Development of Dementia in Old Age

Robert S. Wilson, PhD, Christopher T. Begeny, BA, Patricia A. Boyle, PhD, Julie A. Schneider, MD, and David A. Bennett, MD
Rush Alzheimer's Disease Center and Departments of Neurological Sciences (RSW, JAS, DAB), Behavioral Sciences (RSW, PAB), and Pathology (JAS), Rush University Medical Center, Chicago, IL, USA

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Personality and resilience to Alzheimer's disease neuropathology: A prospective autopsy study

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2Division of Neuropathology, Johns Hopkins University
3Department of Neurology, Johns Hopkins University
4College of Medicine, Florida State University, Tallahassee, FL, USA
5The Brain Bank at Karolinska Institutet, Department of Neurobiology, Care Sciences and Society (NVS), Stockholm, Sweden.
Association of Seafood Consumption, Brain Mercury Level, and APOE e4 Status With Brain Neuropathology in Older Adults

Martha Clare Morris, ScD,
Section on Nutrition and Nutritional Epidemiology, Department of Internal Medicine, Rush University Medical Center, Chicago, Illinois

Brain iron is associated with accelerated cognitive decline in people with Alzheimer pathology

Scott Aytom, Yamin Wang, Ibrahima Diouf, Julie A Schneider, John Brockman, Martha Clare Morris, Ashley J. Bush

1Melbourne Dementia Research Centre, Florey Institute of Neuroscience and Mental Health, and The University of Melbourne, Parkville, Australia
2Rush Institute for Healthy Aging, Rush University Medical Center, Chicago, USA
3CSIRO Health and Biosecurity, Australian E-Health Research Centre, Brisbane, Australia
4Rush Alzheimer Disease Center, Rush University Medical Center, Chicago, USA
5Missouri University Research Reactor, Columbia (Brockman), USA
Cognitive decline after elective and nonelective hospitalizations in older adults

Bryan D. James, PhD, Robert S. Wilson, PhD, Ana W. Capuano, PhD, Patricia A. Boyle, PhD, Raj C. Shah, MD, Melissa Lamar, PhD, E. Wesley Ely, MD, David A. Bennett, MD, and Julie A. Schneider, MD


Figure 2 Rate of decline in global cognition in those who had hospitalization (before and after) or no hospitalization

- Hospitalized (pre)
- Hospitalized (post)
- Not hospitalized
- Average time of hospitalization

Global cognition

Years since baseline
Conclusions

• Alzheimer’s dementia is a complex brain disease with many potential therapeutic targets.

• There are a multitude of risk and protective factors. A better understanding of these is important. For now vascular risk factors important to control.

• Persons without cognitive impairment may have a lot of “subclinical” pathology. Important to recognize but also opportunity for prevention/treatment.

• Pathologically unexplained cognitive change and related risk factors also an opportunity for new prevention and treatment strategies.
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