Senility, Dementia, Hardening of the Arteries and Alzheimer’s Too

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Clinical Neurosciences Track
November 9, 2012
A National Institute on Aging-Supported Alzheimer’s Disease Center

Mission: To translate research advances into improved diagnosis and care for patients with Alzheimer’s disease and related dementias while, at the same time, focusing on the program’s long-term goal—finding a way to cure and possibly prevent AD.
Common Cognitive Changes in Aging

- Benign verbal forgetfulness
- Benign non-verbal forgetfulness
- Decreased attentiveness
- Psychomotor slowing
- Decreased multi-tasking
- Decreased word generation
Trajectory of Cognitive Changes Across the Lifespan

Cognitive Ability (Standard Deviations)

Age groups (years)

Working Memory
Short-term Memory
Long-Term Memory
Speed of Processing
Verbal Knowledge

Park et al., Visuospatial and Verbal Memory Across the Adult Lifespan, Psychol & Aging 17:299-320, 2002
Immigration in Tajikistan
Because of the economic growth of Tajikistan, many people from Kyrgyzstan immigrate to the country. Whereas Kyrgyz people try to preserve their customs, Tajiks want Kyrgyz people to assimilate fully and abandon their customs.
Some Dimensions of Wisdom

• Perspective shifting from one’s own point of view to the point of view of people involved in the conflict;

• Recognition of the likelihood of change;

• Prediction flexibility, as indicated by multiple possible predictions of how the conflict might unfold;

• Recognition of uncertainty and the limits of knowledge;

• Search for conflict resolution; and

• Search for a compromise.
Reasoning about Social Conflict Improves with Age

Relationship of Cognitive Functioning to Age in the Rush ROS and MAP Studies

Age

“GlobCog” Composite

65  70  75  80  85  90  95  100+
Random Sample of Repeated Measures from Rush ROS and MAP Study Participants
Trajectory of Cognitive Changes Across the Lifespan

Cognitive Ability (Standard Deviations)

Diseased Aging - Dementia

Normal Aging

Adapted from: Park et al., Visuospatial and Verbal Memory Across the Adult Lifespan, Psychol & Aging 17:299-320, 2002
A Long List of Possible Causes of Cognitive Decline and Dementia

- **Neurodegenerative Diseases**
  - Alzheimer’s disease
  - *Dementia with Lewy bodies*
  - *Frontotemporal degenerations*
  - Huntington’s disease
  - Progressive supranuclear palsy
  - Corticobasal degeneration
  - Multiple system atrophy
- **Cerebrovascular disease**
  - *Multinfarct, strategic, Binswanger*
  - Cerebral amyloid angiopathy
  - CADASIL
  - Vasculitis
- **Normal Pressure Hydrocephalus**
- **Toxic disorders**
  - Medication toxicity
  - Chronic alcoholism
  - Illicit drugs
- **Autoimmune**
  - Hashimoto’s encephalopathy
  - Sjogren’s syndrome
  - Neuropsychiatric lupus
  - Rheumatoid arthritis, Behcet's
- **Demyelinating disorders**
  - Multiple Sclerosis
  - Leukodystrophies
- **Neoplasia**
  - Paraneoplastic encephalitis
  - Primary, secondary, miliary tumors
  - Neoplastic meningitis
- **Metabolic disorders**
  - Hepatic encephalopathy
  - Hypothyroidism
  - Storage disorders
  - Hypocalcemia
  - Hypoglycemia
- **Nutritional disorders**
  - Vitamin deficiencies (B12, B6, D ...)
- **Mitochondrial disorders**
- **Prion disease**
  - Creutzfeldt-Jakob disease
  - Kuru
  - Gerstmann-Straussler-Scheinker
- **Infection**
  - HIV encephalopathy
  - Neurosyphilis
  - HSV encephalitis
  - PML
  - SSPE
  - Whipple’s disease
- **Psychiatric**
  - Depression, Bipolar
  - Schizophrenia
Major Causes of Dementia in Later Life

- Neurodegenerative Diseases
  - Alzheimer’s disease
  - Dementia with Lewy bodies
  - Frontotemporal degenerations
  - Huntington’s disease
  - Progressive supranuclear palsy
  - Corticobasal degeneration
  - Multiple system atrophy
- Cerebrovascular diseases
  - Hypertensive encephalopathy
- Metabolic disorders
  - Hepatic encephalopathy
- Neoplasia
  - Paraneoplastic encephalitis
  - Primary, secondary, miliary tumors
  - Neoplastic meningitis
- Autoimmune
  - Hashimoto’s encephalopathy
  - Sjogren’s syndrome
  - Neuropsychiatric lupus
  - Rheumatoid arthritis, Behcet’s disease
- Demyelinating disorders
  - Multiple Sclerosis
  - Leukodystrophies
- Other
- Vascular Dementia & Mixed AD/VaD
- Frontotemporal Dementias
Alzheimer’s Disease
"Plaques" and "Tangles"

Auguste D. Alois Alzheimer, 1911
Classical Neuropathological Lesions in Aging

- Plaque & Tangle
- Lewy Bodies
- Pick Bodies
- Bunina Bodies
- Hirano Bodies

- Reactive Astrocytes
- Activated Microglia
- Neuromelanin
- Lipofuscin
- Corpora Amylacea

- Large Vessel Infarct
- Lacunar Infarct
- Microvascular Infarct
- Fibrinoid Necrosis
Biochemical Composition of Major Neurodegenerative Disease Lesions

**β-Amyloid** Diffuse and Neuritic Plaques

**α-Synuclein** Lewy Bodies

**Paired Helical Filament** Tau Neurofibrillary Tangle

**TDP-43** Extranuclear Intracytoplasmic Inclusions and Neurites
Amyloid Precursor Protein Processing, Aβ Oligomers, Fibrils and Plaques
Signature Lesions of Alzheimer's Disease

Amyloid-β Neuritic Plaques

- Neural cell
- Secretion
- Oligomerization
- Aggregation
- Fibrillogenesis

Adapted from schematics courtesy of JQ Trojanowski

PHF-Tau Neurofibrillary Tangles

- Microtubule
- Abnormal phosphorylation
- Tau
- Overactive kinase(s)
- Hypoactive phosphatase(s)
- Neuronal threads
- Axon
- Dendrites
- Senile plaque
- Neuron death

Adapted from schematics courtesy of JQ Trojanowski
Cerebrovascular Disease

Large / medium vessel disease “stroke”

Small vessel disease “lacunar infarct”

Cortical and subcortical “microinfarcts”

from Selnes and Vinters, 2006
# Risk Factors for Sporadic Alzheimer’s Disease in Late Life

<table>
<thead>
<tr>
<th>Non-Modifiable</th>
<th>Modifiable</th>
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<tbody>
<tr>
<td>Age</td>
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<td>Sex</td>
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<tr>
<td>Family history</td>
<td>Hyperlipidemia</td>
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<tr>
<td>APOE 4 gene</td>
<td>Heart disease</td>
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<tr>
<td>Complex genetics</td>
<td>Low education</td>
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<td>Head injury</td>
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<td>Depression</td>
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<td>Negative Affect</td>
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<td>Low mental activity</td>
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## Risk Factors for Sporadic Alzheimer’s Disease in Late Life

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</table>
### Large Vessel Atherosclerosis in Alzheimer’s Disease and Other Neurodegenerative Dementias

<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>n</th>
<th>Age (yrs, SD)</th>
<th>Sex (%F)</th>
<th>PMI (hrs, SD)</th>
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<tbody>
<tr>
<td>Normal</td>
<td>82</td>
<td>66.9 (18.1)</td>
<td>47.6</td>
<td>12.2 (6.9)</td>
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<tr>
<td>Vascular Dementia (incl CAA)</td>
<td>6</td>
<td>84.8 (10.8)</td>
<td>16.7</td>
<td>9.9 (5.6)</td>
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<tr>
<td>Alzheimer's Disease</td>
<td>427</td>
<td>77.1 (10.5)</td>
<td>56.7</td>
<td>12.2 (7.4)</td>
</tr>
<tr>
<td>Tauopathy (FTD-T, Pick's, PSP, CBD)</td>
<td>140</td>
<td>71.9 (10.8)</td>
<td>44.3</td>
<td>13.8 (11.2)</td>
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<tr>
<td>Synucleinopathy (PD, PDD, DLB, MSA)</td>
<td>240</td>
<td>74.3 (10.1)</td>
<td>25.1</td>
<td>13.2 (11.2)</td>
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<tr>
<td>Frontotemporal Lobar Degen- TDP43</td>
<td>76</td>
<td>67.9 (11.5)</td>
<td>46.1</td>
<td>12.3 (8.2)</td>
</tr>
<tr>
<td>Amyotrophic Lateral Sclerosis</td>
<td>85</td>
<td>62.2 (11.1)</td>
<td>36.5</td>
<td>12.9 (7.9)</td>
</tr>
</tbody>
</table>

**Circle of Willis**

Yarchoan et al., in review
Association of Circle of Willis Atherosclerosis in Neurodegenerative Diseases

Frequency and Severity of Atherosclerosis in Neurodegenerative Diseases

Correlations with Neurodegenerative Lesion Ratings

Yarchoan et al., in review
Type II Diabetes - Insulin Resistance

High circulating insulin levels
Metabolic syndrome:
  Abdominal overweight/obesity
  Triglycerides > 150 mg/dl
  HDL cholesterol < 40-50 mg/dl
  BP > 130/85
  Fasting blood glucose 100-125 mg/dl
Epidemiological Studies Associate Alzheimer’s Type Dementia with Type II Diabetes Mellitus (T2D)

Honolulu-Asia Aging Study: Incident dementia with T2D by interview and blood glucose
Total dementia: RR 1.5 [95% CI 1.01-2.2]  Alzheimer's disease: RR 1.8 (1.1-2.9)
[Peila et al., Diabetes 4: 1256, 2002]

Rotterdam Study: Two-year incident dementia in participants with T2D at baseline
Total dementia RR 1.9 (1.3 to 2.8)  Alzheimer’s disease RR 1.9 (1.2 to 3.1)
[Ott et al., Neurology 53:1907, 1999]

Cardiovascular Health Study Cognition Study: Incident dementia
Total dementia: T2D only RR* 1.44 (1.03-2.01); T2D + APOEe4 RR* 3.24 (2.00-5.25)
Alzheimer’s disease: T2D only RR* 1.62 (0.98-2.67); T2D + APOEe4 RR* 4.99 (2.70-9.20)
[Irie et al., Arch Neurol 65:89, 2008]  *adj age, sex, ed, HTN, cholest, tobac, EtOH, BMI, depression, ABI, stroke

North Manhattan: Incident dementia in relation to baseline fasting insulin levels
Total dementia HR* 1.9 (1.3-2.7)  Alzheimer’s disease HR*  2.1 (1.5-3.1)
[Luchsinger et al., Neurology 63:1187, 2004]  *adj age, sex, ed, APOEe4, T2D, HTN, LDL, BMI heart dz, stroke

Rush Religious Orders Study
Alzheimer’s disease HR 1.58* (1.05-2.38)
[Arvanitakis et al., Arch Neurol 61:661, 2004]  *adj age, sex, ed, stroke
Neuronal Expression of IRS-1 pS616 in AD

Normal

Alzheimer’s Disease

from Talbot et al. Journal of Clinical Investigation, 2012
Experimental Evidence of Insulin Resistance Using Postmortem Brain Insulin Stimulation Paradigm

Small brain tissue specimen gradually thawed

50 µm slices while still thawing

Prepare extracts

Incubate tissue slice in ligand or vehicle

Immunoprecipitate for IRb, IRS-1, other molecules

Immunoblot for phospho-epitopes, other molecules to assess activation

Method of H.-Y. Wang

Insulin, etc.

Tissue Slice
Insulin Signaling Pathway Relevant to Alzheimer’s Disease
Heat Map Summary of Semi-Quantitative ICC Results in CA1 in UPenn Cases

### Basic Insulin Signaling Molecules
- IRβ-A
- IRS-1
- PTEN
- Akt1
- GSK-3β

### Phospho-Specific Insulin Signaling Molecules
- IRβ pY
- IRS-1 pS
- IRS-1 pS
- IRS-1 pS
- IRS-1 pY
- IRS-1 pY
- Akt1 pS
- Akt2 pS
- GSK-3β pS
- AS160 pT

### Regulators and Effectors of Insulin Signaling
- mTOR pS
- PKC(ζ/λ) pT
- JNK pT/pY
- IKK pS
- PP2A
- PP2B
- PTP1B

### Alzheimer’s Disease Neuropathological Parameters
- Aβ plaque load
- oAβ plaque load
- NFT density
- Nitrotyrosine
- Neuron Density

Talbot et al., submitted
Linear Regression Models of IRS-1 pS\textsuperscript{616} + Neuron Density in CA1 and Episodic Memory

<table>
<thead>
<tr>
<th>IRS-1 pS\textsuperscript{616}</th>
<th>Age, Sex, Ed</th>
<th>IRS-1 pS\textsuperscript{616}, (\alpha\text{β})</th>
<th>Age, Sex, Ed</th>
<th>IRS-1 pS\textsuperscript{616}, Aβ, Tau, Age, Sex, Ed</th>
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<tbody>
<tr>
<td>(R^2) Adj</td>
<td>0.105*</td>
<td>0.465****</td>
<td>0.542****</td>
<td>0.581****</td>
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<tr>
<td>IRS-1 pS\textsuperscript{616}</td>
<td>-0.137****</td>
<td>-0.112****</td>
<td>-0.109****</td>
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<tr>
<td>(\alpha\text{β}) (Oligomeric)</td>
<td>-1.044*</td>
<td>-1.044*</td>
<td>-0.847</td>
<td></td>
</tr>
<tr>
<td>Tau</td>
<td></td>
<td></td>
<td>-0.030</td>
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</table>

\*p<0.05, \**p<0.01, \***p<0.001, \****p<0.0001

Talbot et al. JCI 2012 d
Metabolic-Vascular-Inflammatory Cascades in Age-Related Brain Failure

“Systems-Level” Processes

- Insulin Resistance
- Inflammation
- Hypertension
- Stress-HPA-ANS Axis

Cellular/Molecular Processes

- Cell ischemia & hypoxia
- Excitotoxicity
- [Ca²⁺]ᵢ dysregulation
- Oxidative and nitrosative stress
- Blood-brain barrier breakdown / Podocyte effacement
- Mitochondrial dysfunction
- Ubiquitin-proteosome activity
- **Protein misfolding**
- Autophagy-lysosome activity
- Cytoskeletal and intracellular trafficking disruption
- Programmed cell death I, II, III
- Transcriptional dysregulation

“Cerebral Failure”

Alzheimer’s, Vascular & Mixed Cognitive Impairment
Rush Religious Orders Study

Archdiocesan Priests of Chicago, IL, Dubuque, IA, Milwaukee, WI
Benedictine Monks of Lisle, IL, Collegeville, MN
Benedictine Sisters of Eerie, PA, Lisle, IL
Capuchins of Appleton, WI
Christian Brothers of Chicago, IL, Memphis, TN
Diocesan Priests of Gary, IN
Dominicans of River Forest, IL
Felician Sisters, Chicago, IL
Franciscan Handmaids of Mary, NY, NY
Franciscans of Chicago, IL
Holy Spirit Missionary Sisters, Techny, IL
Maryknolls of Los Altos, CA, Maryknoll, NY
Norbertines of DePere, WI
Oblate Sisters of Providence, Baltimore, MD
Passionists of Chicago, IL
Presentation Sisters, BVM, Chicago, IL and Dubuque, IA
Sisters of the Holy Family, New Orleans, LA
others...

Rush Memory and Aging Project
Negash et al., in review
Regression Modeling of Cognition in the ROS & MAP Cohorts
Effects of Demographics, Pathology and Distress

<table>
<thead>
<tr>
<th>Age</th>
<th>Age, Sex</th>
<th>Age, Sex, Educ</th>
<th>Age, Sex, Educ, Aβ</th>
<th>Age, Sex, Educ, Aβ, Tau</th>
<th>Age, Sex, Educ, Aβ, Tau, Infarct</th>
<th>Age, Sex, Educ, Aβ, Tau, Infarct, α-Syn</th>
<th>Age, Sex, Educ, Aβ, Tau, Infarct, Psych Distress</th>
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<tr>
<td>R² Adj</td>
<td>0.078</td>
<td>0.078</td>
<td>0.079</td>
<td>0.135</td>
<td>0.345</td>
<td>0.363</td>
<td>0.376</td>
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<td>Parameter Estimates</td>
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<tr>
<td>Age</td>
<td>-0.050****</td>
<td>-0.050****</td>
<td>-0.05****</td>
<td>-0.043****</td>
<td>-0.038****</td>
<td>-0.035****</td>
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<td>Sex (F)</td>
<td>-0.017</td>
<td>-0.015</td>
<td>-0.017</td>
<td>0.070</td>
<td>0.062</td>
<td>0.248</td>
<td>0.083</td>
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<td>Education</td>
<td>0.004</td>
<td>0.012</td>
<td>0.013</td>
<td>0.013</td>
<td>0.012</td>
<td>0.012</td>
<td>0.059****</td>
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<tr>
<td>Amyloid-β</td>
<td>-0.095****</td>
<td>-0.0022</td>
<td>-0.001</td>
<td>-0.004</td>
<td>-0.065*</td>
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<tr>
<td>Tau</td>
<td>-0.071****</td>
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<td>-0.069****</td>
<td>-0.054****</td>
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<td>Infarcts</td>
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<td>-0.380****</td>
<td>-0.280*</td>
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<tr>
<td>α-Synuclein</td>
<td>-0.354**</td>
<td>-0.338*</td>
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<td>Psychological Distress</td>
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Negash et al., in review
Thank you for your interest!

Penn Memory Center and Penn Alzheimer’s Disease Center
Faculty, Staff & Collaborators