Reducing Your Risk of Alzheimer's Disease: Building a Better Brain as We Age

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Religious Orders Study

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How do we Prevent AD?

- Identify risk factors for AD
- Determine biologic pathways linking risk factors to disease
- Develop strategies to prevent AD
Need Studies that Include:

• Large numbers of people without dementia

• Agree to:
  – Donation of blood for genetic testing
  – Detailed assessment of potential risk factors for AD
  – Annual testing to
    • Identify the occurrence of AD
    • Document diagnoses and cognition proximate to death

• How do we get measures of changes in the brain?
  – Brain imaging
  – Brain autopsy
Objectives

• Two clinical-pathologic studies of aging and AD
  – Religious Orders Study
  – Rush Memory and Aging Project
• Common age-related brain pathology
• Implications of mixed pathologies for AD prevention
• Concept of neural reserve
• How to build a better brain as we age
The Religious Orders Study

- Began in 1993
- > 1,135 older nuns, priests, and brothers without known dementia from across the U.S.
- All agreed to annual cognitive and motor testing
- All agreed to brain donation at the time of death
- > 260 have developed AD
- > 360 have developed MCI
- > 485 brain autopsies
The Rush Memory and Aging Project
... because memories should last a lifetime

- Began in 1997
- > 1,335 residents from about 40 retirement communities and senior housing from across the Chicago area
- All agreed to annual cognitive and motor testing, and blood draw.
- All agreed to donate brain, spinal cord, muscle, and nerve at the time of death
- > 200 have developed AD
- > 300 have developed MCI
- > 345 autopsies
Two Studies Include:

• Nearly 2600 people without dementia who agreed to:
  – Donation of blood for genetic testing
  – Detailed assessment of potential risk factors for AD
  – Annual testing to
    • Identify the occurrence of AD
    • Document diagnoses and cognition proximate to death
  – Brain donation
    • More than 830 autopsies to date
Objectives

• Two clinical-pathologic studies of aging and AD
• Common age-related brain pathology
  – AD
  – Cerebral Infarctions
  – Lewy bodies
• Implications of mixed pathologies for AD prevention
• Concept of neural reserve
• How to build a better brain as we age
Normal Brain

Alzheimer’s Disease
Modified Bielschowsky silver stain

Normal Brain
Neurofibrillary Tangles Mediate the Association of Amyloid Load With Clinical Alzheimer Disease and Level of Cognitive Function

Low and high amyloid

One and many tangles

Normal brain

Cerebral infarction (stroke)
Cortical microinfarct
Lewy bodies in substantia nigra

Lewy bodies in hippocampus

Lewy bodies in neocortex
Mixed pathology is most common cause of AD.
Objectives

- Two clinical-pathologic studies of aging and AD
- Common age-related brain pathology
- Implications of mixed pathologies for AD prevention
  - Not all risk factors for clinical AD are related to AD pathology
- Concept of neural reserve
- How to build a better brain as we age
Alzheimer’s Disease

Risk Factors
- Genetic
- Lifestyle

Implications for the prevention of AD

Amyloid Tangles
Infarcts
Lewy bodies

Alzheimer’s Disease
Neuropathologic intermediate phenotypes enhance association to Alzheimer susceptibility alleles

- **APP**
- **PSEN1**
- **PSEN2**
- **APOE**
- Other Genes

- **APOE** and Other Genetic and Environmental Risk Factors

Amyloid plaques
- Neurofibrillary tangles

Neurodegeneration:
- Loss of synapses, neurons, dendrites, dendritic spines

Cognitive Decline

Clinical AD

- Can prevent AD by preventing:
  - AD pathology
  - Infarcts or Lewy bodies

The apolipoprotein E ε2 allele and decline in episodic memory

Neuropathologic intermediate phenotypes enhance association to Alzheimer susceptibility alleles

<table>
<thead>
<tr>
<th>Any APOE ε4</th>
<th>0.365 (0.0363) $9 \times 10^{-24}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any APOE ε2</td>
<td>$-0.200 (0.0461) 1 \times 10^{-5}$</td>
</tr>
</tbody>
</table>
Diabetes Mellitus and Risk of Alzheimer Disease and Decline in Cognitive Function

Diabetes is related to cerebral infarction but not to AD pathology in older persons.

APOE leads to clinical AD through AD pathology
Diabetes leads to clinical AD through infarctions

Objectives

• Two clinical-pathologic studies of aging and AD
• Common age-related brain pathology
• Implications of mixed pathologies for AD prevention
• Concept of neural reserve
  – Neuropathology in persons without dementia
• How to build a better brain as we age
The Neuropathology of Probable Alzheimer Disease and Mild Cognitive Impairment

Pathology common in persons with MCI and those without dementia or MCI.

Concept of neural reserve:

• Individual brains differ in their ability to withstand the effects of brain pathology
Concept of neural reserve:

- Individual brains differ in their ability to withstand the effects of brain pathology
- The same amount of brain pathology does not result in the same amount of memory loss in different people
Neurofibrillary Tangles Mediate the Association of Amyloid Load With Clinical Alzheimer Disease and Level of Cognitive Function

Neurofibrillary Tangles Mediate the Association of Amyloid Load With Clinical Alzheimer Disease and Level of Cognitive Function

Objectives

• Two clinical-pathologic studies of aging and AD
• Common age-related brain pathology
• Implications of mixed pathologies for AD prevention
• Concept of neural reserve
• How to build a better brain as we age
  – Factors related to vulnerability or resilience
Neuropathologic intermediate phenotypes enhance association to Alzheimer susceptibility alleles

- APP
- PSEN1
- PSEN2
- APOE
- Other Genes

- Amyloid plaques
- Neurofibrillary tangles

- Neurodegeneration:
  - Loss of synapses, neurons, dendrites, dendritic spines

- Cognitive Decline

- Infarctions
- Lewy bodies
- Other pathology

How do we build a better brain as we age?

Building a Better Brain

• Vulnerable
  – Depressive symptoms
  – Anxiety
  – Distress proneness
  – Loneliness
  – Harm avoidance

• Resilient
  – Years of education
  – Cognitive activities
  – Physical activities
  – Social activities
  – Conscientiousness
  – Social networks
  – Processing resources
  – Purpose in life
  – Life space
Depressive symptoms (CES-D) (e.g., I felt like everything was an effort, I felt depressed, I felt sad, I could not “get going”).
Depressive symptoms, clinical AD, and cortical plaques and tangles in older persons

Cerebral Infarctions and the Relationship of Depression Symptoms to Level of Cognitive Functioning in Older Persons

Anxiety was assessed with the State-Trait Anxiety Inventory which queries about feelings of anxiety thought to be relatively stable over time.

I feel nervous and restless.
Anxiety and Depression Are Associated with Hippocampal CA3 Dendrite and Spine Density in Older Humans

Anxiety and Depression Are Associated with Hippocampal CA3 Dendrite and Spine Density in Older Humans


Dendritic spines in hippocampus

Graph showing the relationship between Synaptopodin Spine Index and Composite Anxiety-Depression Index.
Proneness to psychological distress is associated with risk of Alzheimer’s disease

Neuroticism refers to the disposition to experience psychological distress

I am a worrier;
I often feel tense and jittery;
I often get angry at the way people treat me;
I often feel helpless and want someone else to solve my problems
Loneliness is a measure of the feeling of social isolation

I experience a general sense of emptiness,
I miss having people around,
I feel like I don’t have enough friends,
I often feel abandoned,
I miss having a really good friend
Loneliness is a trait associated with behavioral inhibition, i.e., a tendency to avoid new situations and aversive stimuli.

Four Subscales:
- anticipatory worry; e.g., “Things often go wrong for me unless I’m careful”
- fear of uncertainty; e.g., “I usually feel tense and worried when I have to do something new and unfamiliar.”
- shyness; e.g., “I am more shy than most people.”
- fatigability; e.g., “I have less energy and tire more quickly than most people.”
Building a Better Brain

- **Vulnerable**
  - Depressive symptoms
  - Anxiety
  - Distress proneness
  - Loneliness
  - Harm avoidance

- **Resilient**
  - Years of education
  - Cognitive activities
  - Physical activities
  - Social activities
  - Conscientiousness
  - Social networks
  - Processing resources
  - Purpose in life
  - Life space
Education modifies the relation of AD pathology to level of cognitive function in older persons

An example of the cognitive scores of two older women (scale: mean = 100, SD = 10, from baseline).

<table>
<thead>
<tr>
<th>Education plaques</th>
<th>score</th>
<th>plaques</th>
<th>score</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 years</td>
<td>0</td>
<td>98.1</td>
<td>18</td>
</tr>
<tr>
<td>15 years</td>
<td>0</td>
<td>96.8</td>
<td>18</td>
</tr>
</tbody>
</table>

The relation of cognitive activity to risk of developing Alzheimer’s disease

The relation of cognitive activity to risk of developing Alzheimer’s disease

<table>
<thead>
<tr>
<th>Model term</th>
<th>Model A</th>
<th></th>
<th></th>
<th>Model B</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>SE</td>
<td>p</td>
<td>Estimate</td>
<td>SE</td>
<td>p</td>
</tr>
<tr>
<td>Time</td>
<td>−0.019</td>
<td>0.010</td>
<td>0.053</td>
<td>−0.010</td>
<td>0.012</td>
<td>0.403</td>
</tr>
<tr>
<td>Time squared</td>
<td>−0.014</td>
<td>0.003</td>
<td>&lt;0.001</td>
<td>−0.015</td>
<td>0.003</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current cognitive activity</td>
<td>0.256</td>
<td>0.024</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current activity × time</td>
<td>0.019</td>
<td>0.008</td>
<td>0.017</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past cognitive activity</td>
<td></td>
<td></td>
<td></td>
<td>0.183</td>
<td>0.034</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Past activity × time</td>
<td></td>
<td></td>
<td></td>
<td>0.027</td>
<td>0.011</td>
<td>0.017</td>
</tr>
</tbody>
</table>

## Cognitive Activities

<table>
<thead>
<tr>
<th>Activity</th>
<th>Age 6</th>
<th>Age 12</th>
<th>Age 18</th>
<th>Age 40</th>
<th>Current</th>
</tr>
</thead>
<tbody>
<tr>
<td>Read to</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Told stories</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Play games</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Time reading/day</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time on homework/day</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit library</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Read newspaper</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Read magazine</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Read books</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Write letter</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Music instruction</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Kept a diary</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Visit museum</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Attend concert, play</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
The relation of cognitive activity to risk of developing Alzheimer’s disease

<table>
<thead>
<tr>
<th>Model term</th>
<th>Estimate</th>
<th>SE</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyloid burden</td>
<td>0.002</td>
<td>0.028</td>
<td>0.943</td>
</tr>
<tr>
<td>Tangle density</td>
<td>-0.016</td>
<td>0.014</td>
<td>0.229</td>
</tr>
<tr>
<td>Braak stage</td>
<td>0.003</td>
<td>0.066</td>
<td>0.964</td>
</tr>
<tr>
<td>Lewy bodies</td>
<td>-0.130</td>
<td>0.222</td>
<td>0.561</td>
</tr>
<tr>
<td>One infarction</td>
<td>-0.304</td>
<td>0.229</td>
<td>0.188</td>
</tr>
<tr>
<td>Multiple infarction</td>
<td>-0.037</td>
<td>0.206</td>
<td>0.859</td>
</tr>
</tbody>
</table>

SOCIAL ENGAGEMENT AND COGNITIVE FUNCTION IN OLD AGE

How often during the past year did you

Go to restaurants, sporting events, play bingo on day trips or overnight trips
do unpaid community/volunteer work
visit relatives or friends houses
participate in groups, such as senior center, social club
Total Daily Activity is Associated With Cognition in Older Persons

<table>
<thead>
<tr>
<th>Date</th>
<th>Activity (Total)</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sat, 13-Aug</td>
<td>755107</td>
<td>131.1</td>
</tr>
<tr>
<td>Sun, 14-Aug</td>
<td>512646</td>
<td>89.0</td>
</tr>
<tr>
<td>Mon, 15-Aug</td>
<td>608995</td>
<td>105.7</td>
</tr>
<tr>
<td>Tue, 16-Aug</td>
<td>697239</td>
<td>121.0</td>
</tr>
<tr>
<td>Wed, 17-Aug</td>
<td>655222</td>
<td>113.8</td>
</tr>
<tr>
<td>Thu, 18-Aug</td>
<td>656111</td>
<td>113.9</td>
</tr>
<tr>
<td>Fri, 19-Aug</td>
<td>577422</td>
<td>100.2</td>
</tr>
<tr>
<td>Sat, 20-Aug</td>
<td>612747</td>
<td>106.4</td>
</tr>
<tr>
<td>Sun, 21-Aug</td>
<td>546006</td>
<td>94.8</td>
</tr>
</tbody>
</table>

Conscientiousness refers to a tendency to be self-disciplined, scrupulous, and purposeful.

I am a productive person who always gets the job done.
The effect of social networks on the relation between Alzheimer’s disease pathology and level of cognitive function in old people: a longitudinal cohort study

Number of relatives (besides spouse and children) and other friends that they saw each month that they felt close to and at ease with and could talk to about private matters and could call upon for help.
Processing resources reduce the effect of Alzheimer pathology on other cognitive systems

**Processing resources:**

Perceptual speed refers to the speed with which mental comparisons are made.

Working memory involves the ability to hold and manipulate information in short-term memory stores.

## Participation in Cognitively Stimulating Activities and Risk of Incident Alzheimer Disease

<table>
<thead>
<tr>
<th>Cognitive Measure</th>
<th>Model Terms</th>
<th>Estimate (SE)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episodic memory</td>
<td>Cognitive activity</td>
<td>0.100 (0.037)</td>
<td>.007</td>
</tr>
<tr>
<td></td>
<td>Time</td>
<td>-0.037 (0.008)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Cognitive activity × time</td>
<td>0.020 (0.012)</td>
<td>.10</td>
</tr>
<tr>
<td>Semantic memory</td>
<td>Cognitive activity</td>
<td>0.221 (0.038)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Time</td>
<td>-0.048 (0.007)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Cognitive activity × time</td>
<td>0.010 (0.010)</td>
<td>.36</td>
</tr>
<tr>
<td>Working memory</td>
<td>Cognitive activity</td>
<td>0.082 (0.041)</td>
<td>.05</td>
</tr>
<tr>
<td></td>
<td>Time</td>
<td>-0.035 (0.005)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Cognitive activity × time</td>
<td>0.021 (0.008)</td>
<td>.007</td>
</tr>
<tr>
<td>Perceptual speed</td>
<td>Cognitive activity</td>
<td>0.211 (0.052)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Time</td>
<td>-0.087 (0.008)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Cognitive activity × time</td>
<td>0.026 (0.012)</td>
<td>.02</td>
</tr>
<tr>
<td>Visuospatial ability</td>
<td>Cognitive activity</td>
<td>0.133 (0.048)</td>
<td>.005</td>
</tr>
<tr>
<td></td>
<td>Time</td>
<td>-0.020 (0.007)</td>
<td>.002</td>
</tr>
<tr>
<td></td>
<td>Cognitive activity × time</td>
<td>0.015 (0.010)</td>
<td>.14</td>
</tr>
</tbody>
</table>

Tendency to derive meaning from life’s experiences and possess a sense of intentionality and goal directedness that guides behavior.

I feel good when I think of what I’ve done in the past and what I hope to do in the future; I am an active person in carrying out the plans I set for myself.
Life space and risk of Alzheimer’s disease, mild cognitive impairment, and cognitive decline in older adults: prospective cohort study

Six zones in the past week


Summary

• AD pathology is common in persons without dementia, and in persons without mild cognitive impairment

• Many factors in addition to AD pathology determine the likelihood of dementia in old age
  – Coexisting brain pathology
    • Infarcts
    • Lewy bodies
  – Life experiences and psychological factors
    • Some increase vulnerability
    • Some increase resilience

• AD is a disease of a lifetime; there are many ways to build a better brain as we age
Future Directions and Other ongoing work:

- Relation of AD pathology to healthcare and financial decision making in persons without dementia
  - Impaired decision making results in part from subclinical AD
- Relation of AD pathology to mobility
  - AD is a poorly recognized cause of gait disturbance
- Relation of genetic factors to AD pathology
  - Genes more strongly related to pathology than cognition
- Nutrition survey
  - You are what you eat
- Relation of factors associated with neural reserve to
  - brain elements needed for cognitive function (e.g., neurons, synapses, dendrites, spines)
  - brain proteins
  - brain epigenome
  - brain imaging
Amyloid Tangles
Alzheimer’s Disease
Unknown neurobiologic indices
Infarcts
Lewy bodies
Parkinsonian signs
Muscle strength
Physical Frailty
Loss of BMI

APOE
Other genetic variants

APOE
Diabetes

Social Networks
Education
Conscientiousness
Cognitive activity
Physical activity
Social activity
Physical activity
Loneliness
Depressive symptoms
Anxiety
Psychological distress
Purpose in life

Impaired Decision Making
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  - brain elements needed for cognitive function (e.g., neurons, synapses, dendrites, spines)
  - brain proteins
  - brain epigenome
  - brain imaging
Genes, Lifestyles, and Crossword Puzzles:

Can Alzheimer’s Disease be Prevented?

National Institute on Aging, Alzheimer’s Disease Education and Referral Center
What can you do to prevent AD?

• Control diabetes and high blood pressure
• Relax, be happy
• Get out and do something new
• Engage in regular:
  – Cognitive activities
  – Physical activities
  – Social activities
• Maintain social ties
• Engage in meaningful, goal directed behavior
• Be diligent
• Start early