

What Have we Learned from Brain Autopsies of Persons with and without Dementia

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14th Annual Mild Cognitive Impairment Symposium
Risk Factors for Cognitive Decline
Miami, FL
January 17, 2016

Acknowledgments

Study Participants in: Religious Orders Study Memory and Aging Project

Faculty and Staff of the Rush Alzheimer's Disease Center,
and collaborators across the USA, Canada, Europe, Israel,
Brazil, India, and China

National Institutes of Health
Alzheimer's Association
Illinois Department Public Health
Elsie Heller Brain Bank Endowment Fund
Robert C. Borwell Endowment Fund

Objectives

- Two clinical-pathologic studies of aging and AD
- What's in an aging brain
- Concept of neural reserve
- Factors that increase or decrease brain vulnerability
- How to build a better brain as we age

The Religious Orders Study

- Began in 1993
- ~ 1,350 older nuns, priests, and brothers without known dementia from across the U.S.
- All agreed to annual clinical evaluation, blood donation at baseline, and repeated on a subset
- All agreed to brain donation
- ~ 500 have developed MCI
- ~ 400 have developed dementia
- ~ 675 brain autopsies



Religious Orders Study: Participating Sites



The Memory and Aging Project ... because memories should last a lifetime

- Began in 1997
- >1,825 older persons without dementia from across northeastern Illinois
- All agreed to annual clinical evaluation and annual blood donation
- All agreed to donate brain, spinal cord, muscle, nerve
- ~ 450 have developed MCI
- ~ 325 have developed dementia
- > 650 autopsies





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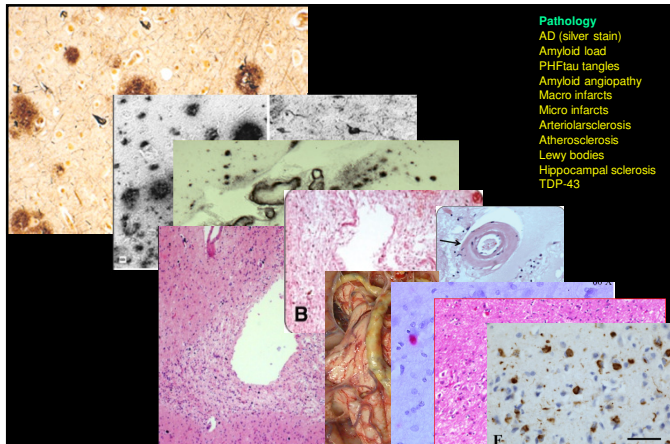
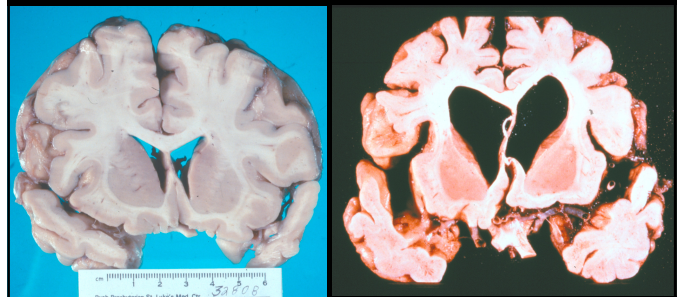
Alzheimer's disease

Normal brain



Normal brain

Alzheimer's disease



By Age 85

- Alzheimer's disease
 - Virtually every brain
- Cerebrovascular disease (stroke)
 - More than half of brains
- Parkinson's disease (Lewy bodies)
 - About 20% (1 in 5) brains
- Frontal-temporal lobar degeneration (TDP-43)
 - About half of brains
- Hippocampal sclerosis
 - About 10% (1 in 10) brains

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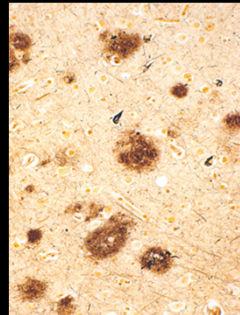
Concept of neural reserve:

- Individual brains differ in their ability to withstand the effects of brain pathology

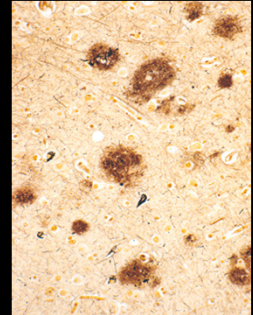
Concept of neural reserve:

- 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

Dementia



No Dementia



Which brain has more AD 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
- **Why do some people with pathologic AD have dementia whereas others do not?**

Objectives

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- **Factors that increase/decrease brain vulnerability**
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Increase Brain Vulnerability

- Coexisting pathologies
 - Cerebral infarctions (stroke)
 - Lewy bodies (Parkinson's disease)
 - TDP-43 (frontal-temporal lobar degeneration)
 - Hippocampal sclerosis
- Medical factors
 - Diabetes
 - Hypertension
 - Anemia
 - Sleep fragmentation
 - Surgical Menopause
 - Chronic kidney disease

Increase Brain Vulnerability

- Psychological factors
 - Emotional neglect in childhood
 - Depressive symptoms
 - Proneness to psychological distress (neuroticism)
 - Anxiety
 - Harm avoidance
 - Loneliness (perceived social isolation)
- Experiential factors
 - Negative social interactions

Emotional neglect in childhood and cerebral infarction in older age

Childhood Adversity (Childhood Trauma Questionnaire) self-report of emotional and physical trauma during the first 18 years of life

Five domains

emotional neglect
parental intimidation
parental violence
family turmoil
financial need

Wilson RS, et al. *Neurology*. 2012;79:1534-39.

Depressive symptoms, cognitive decline, and risk of AD in older persons

Depressive symptoms

I felt like everything I did was an effort
My sleep was restless
I felt sad
I could not get going

Wilson RS, et al. *Neurology*. 2002;59:364-370.

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

Wilson RS, et al. *Neurology*. 2003;61:1479-1485.

Chronic Distress, Age-Related Neuropathology, and Late-Life Dementia

Feelings of anxiety thought to be relatively stable over time

I feel nervous and restless
I wish I could be as happy as others seem to be
I feel like a failure
I get in a state of turmoil as I think over my concerns

Wilson RS, et al. *Psychosomatic Med*. 2007;69:47-53.

Harm Avoidance and Risk of Alzheimer's Disease

Harm avoidance is a trait associated with a tendency to avoid new situations and aversive stimuli

Four subscales:
anticipatory worry
fear of uncertainty
shyness
fatigability

Wilson RS, et al. *Psychosom Med.* 2011;73:690-6

Loneliness and Risk of Alzheimer Disease

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

Wilson RS, et al. *Arch Gen Psych.* 2007;64:234-240.

Negative Social Interactions and Risk of Mild Cognitive Impairment in Old Age

Negative Social Interactions

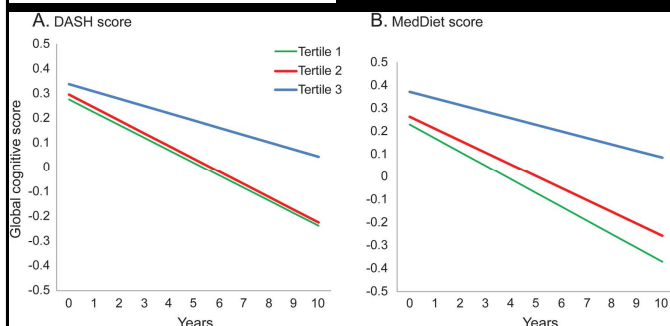
Four domains
neglect or rejection by others
others' unwanted intrusion or advice
failure by others to provide help
unsympathetic or insensitive behavior by others

Wilson RS, et al. *Neuropsychology.* 2015;29:561-570.

Decrease Brain Vulnerability - Resilience

- **Medical factors**
 - MEDI, DASH, and MIND Diet
 - Seafood
- **Psychological factors**
 - Conscientiousness
 - Psychological well-being
- **Experiential factors**
 - Early-life socioeconomic status
 - Formal education
 - Early life cognitive activity, language, and music lessons
 - Late-life Cognitive, Physical, and Social Activity
 - Life-space
 - Social Networks

Relation of DASH- and Mediterranean-like dietary patterns to cognitive decline in older persons



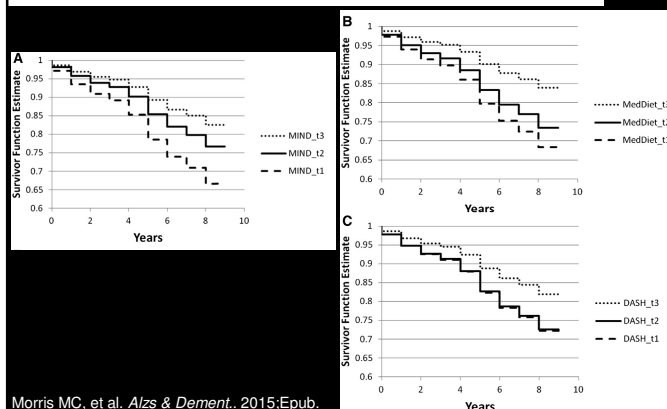
Tangney CC, et al. *Neurology.* 2014;83:1410-6.

MIND diet associated with reduced incidence of Alzheimer's disease

DASH*		MedDiet [†]	
DASH components	Max score	Mediterranean diet components	Max score
Total grains $\geq 7/d$	1	Nonrefined Grains $>4/d$	5
Vegetables $\geq 4/d$	1	Vegetables $>4/d$	5
Fruits $\geq 4/d$	1	Potatoes $>2/d$	5
Dairy $\geq 2/d$	1	Fruits $>3/d$	5
Meat, poultry and fish $\leq 2/d$	1	Full-fat Dairy $\leq 10/wk$	5
		Red meat $\leq 1/wk$	5
		Fish $>6/wk$	5
		Poultry $\leq 3/wk$	5
Nuts, seeds & legumes $\geq 4/wk$	1	Legumes, nuts & beans $>6/wk$	5
Total fat $\leq 27\%$ of kcal	1		
Saturated fat $\leq 6\%$ of kcal	1	Olive oil $\geq 1/d$	5
Sweets $\leq 5/wk$	1		
Sodium ≤ 2400 mg/d	1		
Total DASH Score	10	Alcohol <300 mL/d but >0	5
		Total MedDiet Score	55

Morris MC, et al. *Alz & Dement.* 2015;Epub.

MIND diet associated with reduced incidence of Alzheimer's disease



MIND diet associated with reduced incidence of Alzheimer's disease

MIND	
MIND components	Max score
Whole Grains $\geq 3/d$	1
Green Leafy $\geq 6/wk$	1
Other Vegetables $\geq 1/d$	1
Berries $\geq 2/wk$	1
Red Meats and products $< 4/wk$	1
Fish $\geq 1/wk$	1
Poultry $\geq 2/wk$	1
Beans $> 3/wk$	1
Nuts $\geq 5/wk$	1
Fast/fried food $< 1/wk$	1
Olive Oil primary oil	1
Butter, margarine $< 1 T/d$	1
Cheese $< 1/wk$	1
Pastries, sweets $< 5/wk$	1
Alcohol/wine $1/d$	1
Total MIND Score	15

Source: Morris MC, et al. *Alz & Dement.* 2015;Epub.

Conscientiousness and the Incidence of Alzheimer Disease and Mild Cognitive Impairment

Conscientiousness refers to a tendency to be self-disciplined and scrupulous

I am a productive person who always gets the job done
 I am a very active person
 I have a lot of intellectual curiosity
 I strive for excellence in everything that I do

Wilson RS, et al. *Arch Gen Psych.* 2007;64:1204-12.

The Influence of Cognitive Decline on Well-Being in Old Age

Ryff's Scales of Psychological Well Being:

purpose in life (psychological tendency to derive meaning from life's experiences and possess a sense of intentionality and goal directedness that guides behavior)

self acceptance (positive attitude towards oneself)

autonomy (sense of self-determination and independence)

Wilson RS, et al. *Psych & Aging.* 2013;28:304-13.

Early Life Socioeconomic Status and Late Life Risk of Alzheimer's Disease

Household and county level early life socioeconomic status

Household:

parental education
 parental occupation
 number of children in family

County level:

Duncan socioeconomic status for head of household
 Literacy rate for those over age 6
 Proportion of children age 6-13 in school

Wilson RS, et al. *Neuroepidemiol.* 2005;25:8-14.

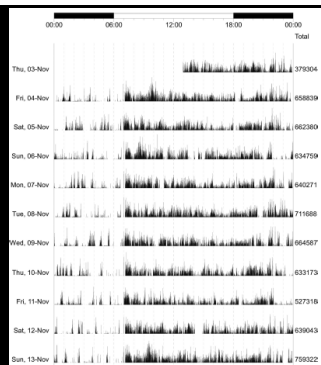
Participation in Cognitively Stimulating Activities and Risk of Incident Alzheimer Disease

Time spent in 7 common activities that involve information processing

Viewing television
 Listening to the radio
 Reading newspapers
 Reading magazines
 Reading books
 Playing games
 Going to museums

Wilson RS, et al. *JAMA.* 2002;287:1742-48.

Total Daily Physical Activity and the Risk of AD and Cognitive Decline in Older Adults



Buchman AS, et al. *Neurology*. 2012;78:1323-1329.

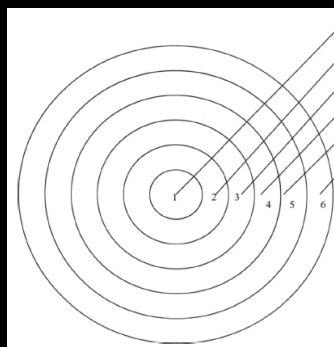
Late-Life Social Activity and Cognitive Decline in Old Age

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

James BD, et al. *J Int Neuropsych Soc*. 2011;17:998-1005.

CORRELATES OF LIFE SPACE IN A VOLUNTEER COHORT OF OLDER ADULTS



Six zones in past week

- Bedroom
- Porch/patio
- Yard/parking lot
- In neighborhood
- Out neighborhood
- Out of town

Inversely scored as
"constricted" life space:
0=not constricted;
6=bedroom bound

Barnes LL, et al. *Exp Aging Res*. 2007;33:77-93.

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 you see each month that you feel close to and at ease with and can talk to about private matters and could call upon for help.

Bennett DA, et al. *Lancet Neurology*. 2006;5:406-412.

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Building a Better Brain as we Age

- Pick your parents well
 - Get a good education including language and music, and don't be emotionally neglected, and make sure you have the right genes
- Chillax, be happy
- Get a good nights sleep
- Avoid people who are downers
- Control vascular disease and risk factors
- Eat a good diet, e.g., DASH, MEDI, MIND, and plenty of seafood
- Be diligent
- Spend time engaged in meaningful, goal directed activities
- Engage in regular cognitive, physical, and social activities
- Strengthen and maintain social ties
- Get out more, explore new things
- And even if you do all of this...