Maintaining Cognitive Health: Prevention of Alzheimer’s Disease and Related Disorders

William Rodman Shankle, MS MD FACP
The Judy and Richard Voltmer Chair For Memory & Cognitive Disorders
Hoag Neurosciences Institute
Director, Orange County Vital Aging Program
Research Fellow, UC Irvine Cognitive Science Department
Chief Medical Officer, Medical Care Corporation

OCBrain.org
Disclosure

Affiliation/Employment
• Medical Director, Shankle Clinic
• Chief Medical Officer, Medical Care Corporation
• Hoag Neurosciences Institute
• Dept of Cognitive Sciences, UC Irvine

Grants
• Baxter Healthcare
• Unihealth Foundation
Overview

- The Structural Basis of Higher Cognitive Function
- Effects of Aging on Cognition and on Synapses
- Spectrum of Normal Aging, Mild Cognitive Impairment, & Dementia
- Causes of Mild cognitive Impairment
- Risk Factors of Cognitive Impairment and Dementia
- The impact of lifestyle intervention on cognition
- A Successful Program To Help Prevent and Delay Onset and Progression of Cognitive Impairment and Dementia

OCBrain.org
The Structural Basis of Higher Cognitive Function

OCBrain.org
The evolved frontal neocortex created a quantum leap in cognitive skills, including:

- **Diverse Stone Tools**
- **Religion**
- **Language**
- **Shared Economy**
- **Kinship Relations**
- **Image Making**

---

### The Evolution of Cognition

**Today**

- **Homo Sapiens**
- **Upper Paleolithic**

35,000 years ago
- **Transition**
- **45,000 years ago**

**Homo Neanderthalensis**

- **Middle Paleolithic**
- **220,000 Years ago**

---

**Frontal Neocortical Expansion**
Cave drawings were repeatedly discovered for centuries before 1863.

The drawings were believed to be of very recent origin because “art was not possible before modern man”, who according to some religions, was created on October 23, 4004 BC.

Darwin’s “Origin of Species” made it possible, to perceive that art and creativity began in humans 30,000 years ago.
COMPLEX BRAIN FUNCTION DEPENDS ON CONNECTIVITY

NUMBER OF BRAIN CELL CONNECTIONS (SYNAPSES): CONSTANT ACROSS MONKEYS.

IN HUMANS, DENSITY OF CONNECTIONS PER NEURON TRIPLES.
The Effects of Aging on Synapses

OCBrain.org
Aging Lowers Threshold for Memory Impairment

Number of Brain Connections Declines with Age. Physical Exercise and Learning Counteract This Decline

Duan et al. Cerebral Cortex Sep 2003, V 13 N 9
Aging Makes Brains Less Spontaneously Active

Spontaneous Brain Cell Activity Decreases

This Makes It Harder For Brains To Stimulate Function
Thus, Age Increases Risk For Cognitive Impairment


OCEBrain.org
The Effects of Aging on Cognition
Effects of Aging on Cognition

Cognitive Decline Begins By 45 Years Old
Most Cognitive Abilities Decline with Age By 33%-50%

Singh-Manoux et al. Timing of onset of cognitive decline: BMJ 2012;344
The Spectrum of Normal Aging, Mild Cognitive Impairment and Dementia

OCBrain.org
Progression from Normal Aging to Dementia: Alzheimer’s Disease

The Functional Assessment Staging Test (FAST)

Normal Aging
- Normal Aging (FAST 1)
- Subjective Decline (FAST 2)

Mild Cognitive Impairment
- Mild Cognitive Impairment (FAST 3)

Dementia
- Mild Dementia (FAST 4)
- Moderate Dementia (FAST 5-6)
- Severe Dementia (FAST 7)

Years of Symptoms
- Prevention

Risk factor management is associated with a 50% reduction in AD risk - 3 to 5 year delay.

Early Detection and Treatment

Treatment of AD Mild Cognitive Impairment & Dementia with Namenda + an AchE Inhibitor (Exelon, Galantamine, Aricept) delays progression by 5-6 years if detected and treated early.

Adding in AD risk factor management can delay AD onset & progression by 8-11 years, which would eliminate dementia from the average rate of progression.

Such a delay would reduce direct, dementia related Medicare costs by $85,000 per affected person, or by approximately $103 billion for the current cohort of Californians with MCI.

OCBrain.org
The Economic Challenge: Demented Patients Are Expensive

<table>
<thead>
<tr>
<th>Payment Source</th>
<th>Beneficiaries with ADRD Dementia</th>
<th>Beneficiaries without ADRD Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
<td>Community-Dwelling</td>
</tr>
<tr>
<td>Medicare</td>
<td>$19,820</td>
<td>$17,651</td>
</tr>
<tr>
<td>Medicaid</td>
<td>10,120</td>
<td>222</td>
</tr>
<tr>
<td>Uncompensated</td>
<td>273</td>
<td>392</td>
</tr>
<tr>
<td>HMO</td>
<td>994</td>
<td>1,543</td>
</tr>
<tr>
<td>Private insurance</td>
<td>2,262</td>
<td>2,485</td>
</tr>
<tr>
<td>Other payer</td>
<td>906</td>
<td>164</td>
</tr>
<tr>
<td>Out-of-pocket</td>
<td>9,368</td>
<td>3,167</td>
</tr>
<tr>
<td>*<em>Total</em></td>
<td><strong>$43,847</strong></td>
<td><strong>$25,804</strong></td>
</tr>
</tbody>
</table>

Sources: Alzheimer’s Disease Facts and Figures (2012)
Table 7: Average Annual Per-Person Payments for Health Care and Long-Term Care Services, Medicare Beneficiaries Age 65 and Older, with and without Alzheimer’s Disease and Other Dementias and By Place of Residence, 2008 Medicare Current Beneficiary Survey, 2011 Dollars

OCBrain.org
Mild Cognitive Impairment, The Precursor To Dementia Affects 1 out of 4 Californians Over 65 Years Old

Medicare Direct Costs If Not Detected Early and Treated

1 of every 4 Californians 65 years and older, or 1.2 million people, are estimated to have mild cognitive impairment (MCI)\(^1,2\), and will be demented for 7 years if not detected early and treated.\(^3\)

The dementia-related, direct Medicare costs of this cohort of 1.2 million Californians without early detection and treatment will be $103 billion over 7 years, or $15 billion/year.\(^3\)

In Orange County alone, 80,000 persons have MCI, 2/3 of them do not know they have it\(^4\).

Without early detection and treatment, dementia related direct Medicare costs in Orange County will be $7 billion, or $1 billion per year of dementia.

\(^1\)Trenkle et al. J. Alzheimer’s Disease. 2007;11(3):323-35
Reducing Dementia Related, Direct Medicare Costs Through Cognitive Healthcare

Dementia Related, Direct Medicare Costs for Current Cohort of 1.2 million Californians with Mild Cognitive Impairment, Based on Method of Assessing Cognition

<table>
<thead>
<tr>
<th>Cognitive Assessment Method</th>
<th>Number (%) of Subjects Delayed</th>
<th>Dementia Related Increase in Direct Medicare Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Assessment</td>
<td>0</td>
<td>$103 Billion</td>
</tr>
<tr>
<td>Subjective Assessment</td>
<td>500,000 (39%)</td>
<td>$73 Billion</td>
</tr>
<tr>
<td>Objective Assessment</td>
<td>1,160,000 (97%)</td>
<td>$28 Billion</td>
</tr>
</tbody>
</table>
Causes of Mild Cognitive Impairment and Dementia
Poorly Controlled Chronic Medical Conditions Often Cause Mild Cognitive Impairment

**Chronic Pain**
- Cancer

**Iatrogenic**
- Anesthesia, Surgery
- Chemotherapy, Radiation
- Medications (Anxiolytics, Antipsychotics, Anticholinergics)

**Hormonal**
- Parathyroid
- Thyroid
- Adrenal
- Hysterectomy, Menopause, Low Estrogen
- Andropause/Low Testosterone

**Nutritional**
- B12, folate, Vitamin D

**Hypoxia**
- Pulmonary Diseases
- Anoxic Events
- Anemia

**Ischemia**
- Cardiac
- Cerebrovascular
- ASVD, Hyperlipidemia
- Hypertension
- Diabetes
- Homocysteinemia
- Anemia

**Metabolic**
- Kidney Diseases
- Seizures
- Dehydration

**Infection**

**Trauma**

**Alcohol Abuse**

**Sleep Disorders**

**Psychiatric**

**Degenerative**
- Alzheimer’s
- Lewy Body/Parkinson’s
- Frontal Temporal

Most Causes Are Treatable, Including Alzheimer’s Disease
If not detected and treated, most causes of mild cognitive impairment will progress to the dementia stage.

OCBrain.org
98% of Normal Aging Persons Have Alzheimer’s, Parkinson’s, or Small Strokes in Small Amounts

Demented persons have 3 times more AD or Parkinson’s lesions or small strokes in their brains than normal aging persons.


OCBrain.org
Reducing The Accumulation of These Lesions and Small Strokes is Key to Preventing Dementia

If we can prevent accumulation of AD, Parkinson’s and small strokes, we can significantly reduce the percentage of persons who become demented.


OCBrain.org
Risk Factors of Mild Cognitive Impairment and Dementia

OCBrain.org
Factors That Increase Abnormal Beta Amyloid and Tau Production in Animal Models

- Genetics
- Head Trauma\(^{3a,3b,8}\)
- Stroke\(^{1,2}\)
- Heart Disease\(^{1,2}\)
- Hypertension\(^{11}\)
- Idiopathic Hydrocephalus\(^{10}\)
- Iron Load\(^{6}\)
- Diabetes\(^{5}\)
- Seizures\(^{4}\)

Factors That Decrease Abnormal Tau and Beta Amyloid and Increase Neurogenesis

- Cognitive Exercise\(^{15}\)
- Physical Exercise\(^{14}\)
- Alcohol Use\(^{7}\)

Reference Slide is Available at End of Lecture

OCBrain.org
Preventing Cognitive Impairment and Dementia Due To Parkinson’s Disease Pathological Lesions

Factors That Increase alpha Synuclein in Animal Models

- Alcohol, Smoking, Caffeine Consumption
- Cleaning Agents (Trichloroethylene)
- Low HDL, High Cholesterol
- Stroke
- Hypoxia

Risk Factors Associated with Cognitive Impairment and Dementia

Most of these Risk Factors, when well managed, reduce production of the lesions of AD, Parkinson’s disease, and stroke.

- High Cholesterol
- Stroke
- Heart Disease
- Hypertension
- Diabetes
- Obesity
- Low Education
- Head Trauma
- Genetics
- Aging
- Cancer
- Certain Medication
- Substance Dependence
- Chronic Stress
- Untreated Depression
- Poor Sleep Quality
- Certain Medication
- Diet
- Physical Exercise
- Brain Exercise
- Alcohol Consumption

OCBrain.org
The Impact of Lifestyle Intervention on Cognition

OCBrain.org
Preventing Dementia due to Alzheimer’s Disease

Estimated Percent and Number of Alzheimer's Disease Cases That Could Be Prevented in the USA Through Risk Factor Modification

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Prevalence</th>
<th>Relative Risk</th>
<th>Potential Risk Reduction</th>
<th>No. of Cases Preventable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Inactivity</td>
<td>33%</td>
<td>1.82</td>
<td>21%</td>
<td>1,115,000</td>
</tr>
<tr>
<td>Low Education</td>
<td>13%</td>
<td>1.59</td>
<td>7%</td>
<td>386,000</td>
</tr>
<tr>
<td>Smoking</td>
<td>21%</td>
<td>1.59</td>
<td>11%</td>
<td>574,000</td>
</tr>
<tr>
<td>Mid-Life Obesity</td>
<td>13%</td>
<td>1.6</td>
<td>7%</td>
<td>386,000</td>
</tr>
<tr>
<td>Depression</td>
<td>19%</td>
<td>1.9</td>
<td>15%</td>
<td>781,000</td>
</tr>
<tr>
<td>Mid-Life Hypertension</td>
<td>14%</td>
<td>1.61</td>
<td>8%</td>
<td>425,000</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9%</td>
<td>1.39</td>
<td>3%</td>
<td>174,000</td>
</tr>
</tbody>
</table>

**Combined**          | **54%**    |               |                          | **2,866,951**            |

1Barnes et al. Lancet Neurol. 2011 September ; 10(9): 819–828

Managing modifiable AD risk factors associates with a 50% reduction in risk of developing AD.

OCBrain.org
Preventing Dementia Due to Alzheimer’s Disease: Potential Impact of Risk Factor Modification

1 Barnes et al. Lancet Neurol. 2011 September; 10(9): 819–828
Higher Education (≥8 years) reduces dementia risk by 50%, even in persons with the major genetic risk for AD—the apoE4 gene.  

Autopsy studies of Wernicke’s Area (language comprehension) show longer, bushier neuronal trees in aging persons with higher education.  

Synaptic Protection via Education Reduces Dementia Risk


OCBrain.org
Use-Dependent Plasticity: Cognitive and Physical Exercise

Environmentally Enriched

Dendritic Branching
Synapse Density

Environmentally Deprived

Dendritic Branching
Synapse Density

Enriched Activity Protects The Synapses Activated via Use-Dependent Plasticity:
Use It or Lose It

OCBrain.org
Use-Dependent Plasticity: A Key To Brain Protection

Hippocampal Long Term Potentiation (LTP)
Cognitive and Physical Exercise Lowers Beta Amyloid Plaques of Alzheimer’s Disease

Typical Activities: reading books/newspapers, writing letters or e-mails, going to library, playing games.
Level of Cognitive Activity: High: daily-weekly. Middle: less than weekly-monthly : Low: less than monthly

Cognitive and Physical Exercise Generate New Hippocampal Neurons


OCBrain.org
Creative, or Problem Solving Maximally Activates Brain Areas

Brain Areas Active During Creativity & Problem Solving

NeuroImage. 2012. 59:772-780

OCBrain.org
A Successful Program To Help Prevent and Delay Onset of Cognitive Impairment and Dementia

The Orange County Vital Brain Aging Program

OCBrain.org
Enabling Healthy Brain Aging in Aging Community

Educated Public

Trained PCPs

Community Assessment Service

OCBrain.org
**National Alzheimer’s Project Act: NAPA (2012)**

**Chair: Ronald Petersen, PhD MD:** Cadieux Director, Mayo Alzheimer’s Disease Research Center

- Prevent and Effectively Treat Alzheimer’s Disease by 2025.
- Optimize Care Quality and Efficiency.
- Expand Support for People with AD and Their Families.
- Enhance Public Awareness and Engagement.
- Track Progress and Drive Improvement.

---

**Orange County Vital Brain Aging Program (2010)**

- Prevent and Effectively Treat Alzheimer’s Disease by 2025.
- Optimize Care Quality and Efficiency.
- Expand Support for People with AD and Their Families.
- Enhance Public Awareness and Engagement.
- Track Progress and Drive Improvement.

[OCBrain.org](http://OCBrain.org)
The Orange County Vital Brain Aging Program: UniHealth Foundation Funding From 2010 to 2016

OCVAP’S KEY COMPONENTS

OCVAP

Community Partners Media Outreach

Public Education
- Seminars
- In-Person Assessment

Web Portal
- Self Assessment
- Educational Contents
- Newsletter

Outcome Analysis

Physician Educacon
- CMEs
- Assessment Tools
- Physician Network
- Expert Panel

OCBrain.org
Over 7,000 People Have Had Their Annual Memory Checkup via OC Vital Brain Aging Program

Most Are Reassured

Assessment Results

% Normal vs. % Impaired

Normal

Impaired

Age Group

<45 45-54 55-64 65-74 75-84 85-94 95=<

Assessment* Results

*Assessment using MCI Screen only, and does not include assessments done using other tools.

Over 7,000 People Have Had Their Annual Memory Checkup via OC Vital Brain Aging Program

Most Are Reassured

OCBrain.org
OCVital Brain Aging Case: Severe Stress

59 Year Old Businessman Before and 1 Year After Treatment of Severe Stress

Memory Performance Score

Severe Stress Resolved

Severe Stress

2011

2012

OCBrain.org
OCVital Brain Aging Case: Depression

71 Year Old Lady Before and 1 Year After Treatment of Depression

Memory Performance Score

- Depression Resolved
- Depressed
OCVital Brain Aging Case: Sleep Apnea

70 Year Old Man  Before and 1 Year After Treatment of Sleep Apnea

Memory Performance Score

- Sleep Apnea
- Sleep Apnea Controlled

OCBrain.org
The Steps To Managing Cognitive Health

- Take the online questionnaires to assess & manage risk factors
- Take a sensitive memory test annually after 50 years old
- Repeat each year
- If a memory problem is found, have it diagnosed and treated as early as possible
OC Vital Brain Aging Program Goal: Individualized ADRD Prevention

Subjects

Risk Factors

Interventions

Biomarkers

Tailor Prevention Prescription For a Given Set of Risk Factors

Causality Methods Research

Commentary on “Developing a national strategy to prevent dementia: Leon Thal Symposium 2009.” Methodologic considerations for preventing Alzheimer’s disease by 2020

Shankle WR. Alzheimer’s & Dementia 6 (2010) 145-146

OCBrain.org
What’s Next?
Measuring the Neurofibrillary Tangles of AD:
The Tau PET Scan

Normal Aging          MCI AD

Mild Dementia AD      Severe Dementia AD

1DT Chien, S Bahri, AK Szardenings, JC Walsha, F Mua, MY Sub, WR Shankle, A Elizarov, HC Kolb Early Clinical PET Imaging Results with the Novel PHF-Tau Radioligand [F-18]-T807. Journal of Alzheimer’s Disease 34 2013: 457–468

OCBrain.org
Thank you to OC Vital Brain Aging donors...

Judy & Richard Voltmer
Roswitha Smale, Ph.D.
The Elliott Family Foundation

UniHealth Foundation
Patricia and Eugene Hancock
Lin Auer

For more information about supporting Vital Brain Aging, contact Christy Ward at (949) 764-7215 or christy.Ward@hoag.org or visit www.hoaghospitalfoundation.org
Causes of Abnormal Tau and Beta Amyloid Production
Summary

- The Neuroanatomical Basis of Higher Cognitive Function
  - Determined by synaptic connectivity and numbers of neurons.

- Effects of Aging on Synapses and on Cognition
  - Modifiable. Associated with levels of Physical and Cognitive Exercise

- The Spectrum of Normal Aging, Cognitive Impairment and Dementia
  - 30 Years are Asymptomatic, 15 Years are symptomatic (Mild Cognitive Impairment and Dementia)
  - Dementia increases direct healthcare costs by $12,000 (160%) per affected person per year.

- Etiologies of Cognitive Impairment and Dementia
  - 98% of normal aging persons have Alzheimer’s, Parkinson’s and/or Stroke pathology
  - Cognitive impairment is determined by the cumulative pathological load of these and other lesions.
  - More than half of cases of cognitive impairment are not due to Alzheimer’s Disease.
  - Poorly controlled chronic medical conditions are a common etiology of cognitive impairment.

- The Impact of Lifestyle Intervention on Cognition
  - There are strong associations of reduced risk of cognitive impairment with lifestyle interventions.

- The Epidemiology of Cognitive Impairment and Dementia:
  - Causal risk factors operate by modifying the pathological lesion burden.
  - Causality Analysis can help discriminate causal from associated risk factors.
  
  OCBrain.org