Biological Underpinnings and Cognitive Expression of Brain Aging

Po H. Lu, Psy.D.
K30 Presentation
December 15, 2009

Mentors: George Bartzokis, M.D.
Paul Thompson, Ph.D.
Overview

• Neuropsychology
• Alzheimer’s disease
• Cognitive changes associated with aging
• White matter changes associated with aging
• Structural-functional relationships
Definition of Neuropsychology

- The study of brain-behavior relationships
- Uses standardized measures to characterize the cognitive and behavioral changes associated with a variety of disorders
Domains of Assessment

- General intellectual functions
- Attention and concentration
- Information Processing Speed
- Language
- Visuospatial skills
- Learning and Memory
- Executive functions/Frontal systems
- Mood
Purpose of Neuropsychological Assessment

- Standardized and **objective** measurement based on established norms
- Aid in differential diagnosis
- Document baseline of functioning
- Make recommendations for:
  - Cognitive rehabilitation techniques
  - Ability for independent living
  - Additional Treatment modalities
Alzheimer’s Disease: Risk Factors

- Age
- ApoE-4 genotype
- Female gender
- Hypercholesterolemia
- Diabetes
- Head injury
- Psychological stress
- Hypertension
- Smoking
Criteria for Diagnosis of Probable Alzheimer’s Disease (NINCDS-ADRDA)

- Dementia established by clinical examination
- Deficit in 2+ areas of cognition (memory required) of at least 12 months in duration
- Gradual onset and progression
- Absence of other systemic disorder or brain disease that can account for the cognitive deficits
Amyloid Plaques and Neurofibrillary Tangles
Age is the Greatest Risk for Alzheimer’s Disease

AD Statistics

5,200,000
Associated Costs: $148 Billion

- $91 billion
- $36.5 billion
- $21 billion

Projected Outcomes

Facts and Figures, Alzheimer’s & Dementia. 4:110-133.
Projected Cost of AD

Cost (billions of U.S. $)

Year

2000 2015 2050

Current Treatment Options

- Acetylcholinesterase Inhibitors
  - Aricept - Donepezil (1996)
  - Exelon - Rivastigmine (2000)
    - New patch formulation of Exelon
  - Razadyne (formerly Reminyl) - Galantamine (2001)
- Namenda - Memantine
  - Most recently approved (January 2004)
  - Moderate to severe AD (MMSE ≤ 15)
The Aging Process
Cognitive Changes Associated with Aging

• Slowing in cognition is the best documented and replicable behavioral phenomena of aging

• Simple reaction time shows gradual incremental slowing beginning at age 30 (Gottsdanker 1982; Wilkinson and Allison 1989)

• Speed in performance of complex activities shows an accelerated rate of slowing after age 60 (Cerella et al. 1980)
Changes in other Cognitive Abilities

• Diminished learning ability and delayed recall (memory) of information with age (remote memory for overlearned information tends to be less compromised)

• Gradual age-related decrements in complex problem solving and visuospatial skills

• In contrast, simple attention span and verbal abilities are generally resistance to the regressive effects of aging
Longitudinal Changes in Six Cognitive Abilities

Schaie 2005
Theory of Processing Speed (Salthouse 1996)

- Increased age in adulthood is associated with decreased processing speed
- Age-related influences on many cognitive abilities are attenuated after statistical control of measures of speed
Conclusions

• Processing speed is the leading indicator of cognitive aging (Finkel et al. 2007)

• Slowed processing speed underlies age-related changes decrements in other cognitive abilities such as memory (Salthouse 1998) and executive functioning (2000)
Types of Processing Speed

- **Reaction time** - responding quickly to visual stimuli through manual keypress
- **Perceptual Speed** - speed of responding with simple content often involving simple search, comparison, and substitution
- **Psychomotor speed** - drawing lines in specified locations, finger tapping
- **Decision Speed** - time to respond with moderately complex content

Salthouse 2005
Trailmaking Test - Part B
**Digit Symbol Substitution**

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>─</td>
<td>─</td>
<td>✗</td>
<td>┼</td>
<td>∧</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2</th>
<th>1</th>
<th>3</th>
<th>4</th>
<th>2</th>
<th>5</th>
<th>2</th>
<th>4</th>
<th>1</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>─</td>
<td>─</td>
<td>✗</td>
<td>┼</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Myelin and Saltatory Conduction

- Myelinated axon
- Node of Ranvier
- Myelin sheath
- Spread of depolarization
- Cell body (soma)
- Unmyelinated axon
- Action potential

© 2002 Encyclopædia Britannica, Inc.
Gray-to-White Matter Ratio over Lifespan
White Matter and Gray Matter on Inversion-Recovery Image

Bartzokis et al. Arch Gen Psychiatry 2001
White Matter and Gray Matter Volume over Lifespan

Bartzokis et al. *Arch Gen Psychiatry* 2001
Imaging and Postmortem
Myelin over the Lifespan

Kaes, 1907, adapted and reproduced in Kemper (1994)
Myelin Integrity

- Small changes in amount of water (i.e. CSF) in the tissue can be detected and quantified by MRI as it alters transverse relaxation time ($T_2$; measured in milliseconds).

- Transverse relaxation time transformed into transverse relaxation rate or $R_2$ by calculating the reciprocal of $T_2$ ($x$ 1000 ms/s to convert to seconds$^{-1}$)

- Myelination reduces white matter water content thereby increasing $R_2$; myelin breakdown increases tissue water and decreases $R_2$
White Matter Regions of Interest
Lifespan Trajectories of R2 in 3 White Matter Regions

Lifespan Trajectories of Processing Speed Performance and Myelin Integrity
Specific Aims

We will be bringing back the subjects in the cross-sectional analysis for re-scanning and re-testing. Using prospective data:

• Specific Aim #1: To characterize the age-related change in myelin integrity in late myelinating regions
• Specific Aim #2: To examine the relationship between change in processing speed with change in myelin breakdown
• Specific Aim #3: To demonstrate that age-related decline in processing speed is mediated by breakdown in myelin integrity
• Specific Aim #4: To demonstrate that age-related decline in verbal memory is mediated by processing speed and myelin integrity
Cross-sectional Results

$r = .22, p = .008$
Mediation Modeling
(Baron & Kenny 1986)

Step 1: Significant effect of IV on DV
Step 2: Significant effect of IV on Mediator
Step 3: Significant effect of Mediator on DV when controlling for IV
Step 4: The direct effect of IV on DV is not statistically significant when controlling for the Mediator (path c’ should be zero)
Mediation of Late-Myelinating $R_2$ on Age-Speed Relationship

![Diagram showing mediation effects between AGE, LMR$_2$, and SPEEDZ]

- (a) $B = -0.052$, s.e. = 0.012, $p = 0.0001$
- (b) $B = 0.831$, s.e. = 0.359, $p = 0.027$
- (c) n.s. ($p = 0.54$)
- $B = -0.063$, s.e. = 0.026, $p = 0.020$
Future Direction: Complex 3-Path Model