Assessing Cognition

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• **Topic:** *Cognitive Aging*

• Assessing Cognition

• Diagnosing Cognitive Impairment
  – Dementia Diagnoses
    • Symptoms & Neuropathology

• Current State of the Art in the Clinic

• Midlife Risk Factors for Late-life Cognitive Impairment
Cognition

• Cognition is the most important determinant of health quality of life and functional ability in older age (Gaugler et al., 2009)

• At any time, diminished cognitive function can cause significant psychological, social, and economic hardship (Athilingam and King, 2007)

• The US population is ageing fast!
• Number of demented individuals expected to quadruple within the next 50 years
• Cost of care already exceeding $150 billion/ year
Neuropsychological Assessment

- Cognition
  - Global Cognitive Functioning
  - Memory
  - Language
  - Attention
  - Executive Functioning
- Sensory Function
- Activities of Daily Living
- Neurobehavioral Symptoms
- Brain Integrity
Localizing Brain Function

Phrenology

Functional Magnetic Resonance Imaging (fMRI)
Diagnosing Cognitive Impairment

• Dementia vs. Mild Cognitive Impairment
  – Impaired Memory +
  – One other area of cognition
  – Impaired Activities of Daily Living
  – Rule out reversible causes of cognitive impairment
  – Subjective Memory Complaint
  – Corroboration by Informant
  – Impaired Memory
  – Intact Activities of Daily Living
  – Rule out reversible causes of cognitive impairment

• Most Common Dementias
  – Alzheimer’s Disease (AD)
  – Vascular Dementia (VaD)
  – Dementia with Lewy bodies (DLB)
  – Frontotemporal Dementia (FTD)
  – Prion Diseases
Alzheimer’s Disease (AD)

- The most common form of dementia (75%)
- Affects 30% of all individuals over age 85
- Clinical Symptoms:
  - Prominent memory impairment
  - Followed by language, motor control, gait disturbance
  - Slow progression
- Pathologic hallmarks:
  - Atrophy
  - Plaques & tangles
Alzheimer’s Disease

On the Surface

Under the Microscope

Neuritic Plaque
Vascular Dementia (VaD)

- Caused by cerebral ischemia (stroke)
- Clinical Symptoms:
  - Prominent executive dysfunction
  - Less prominent memory/language impairment as compared with AD
  - Unilateral sensory or motor dysfunction
- Rarely appears in its pure form (3%)
- Often contributes to the development of Alzheimer’s disease
- Pathologic hallmark:
  - Cerebrovascular lesions
Vascular Dementia (VaD)

- Hemorrhagic Stroke: Hemorrhage/blood leaks into brain tissue
- Ischemic Stroke: Clot stops blood supply to an area of the brain

Imaging Techniques:
- CT
- MRI
Frontotemporal Dementia (FTD)

- Relatively Rare
- Heterogeneous
- Clinical Symptoms:
  - Profound changes in personality
  - Relatively early onset
  - Faster progression
- Pathologic hallmark:
  - Circumscribed atrophy of the frontal lobes
  - Sometimes neuronal inclusions
Frontotemporal Dementia (FTD)

On the Surface

Under the Microscope

Pick Bodies
Dementia with Lewy Bodies (DLB)

- Prevalence 10-15% of all cases
- Parkinson’s Spectrum Disorder
- Clinical Symptoms:
  - Persistent memory impairment
  - Fluctuating cognition
  - Recurrent visual hallucinations
  - Spontaneous Parkinsonism
- Pathologic hallmark:
  - Atrophy
  - Lewy Bodies
Dementia with Lewy Bodies (DLB)

On the Surface

Under the Microscope
Prion Diseases (e.g., Mad Cow Disease)

- Extremely rare
- Heterogeneous (BSE, CJD, K/Juru)
- **Infectious**
- Clinical Symptoms
  - Altered mental state
  - Extremely fast progression
- Pathologic hallmark:
  - Atrophy
  - Spongy appearance of the brain matter
Prion Diseases

On the Surface

Under the Microscope
State of the Art in the Clinic

• Diagnosis is based on clinical symptoms
• No specific \textit{in vivo} biological markers (except for VaD)
• Approximately 90\% accurate
• Limited treatments are available for AD, DLB, and VaD but not for FTD or CJD
• \textbf{No cures}
MRI Biomarkers: Atrophy

Normal Brain  
FTD Brain  
AD Brain
MRI Biomarkers: White Matter Lesions
What then?!?

- Search for modifiable risk factors at midlife
- Focus on prevention
Fighting Nears Tripoli, Where Qaddafi Keeps Grip on Power
By KAREEM FAHIM and DAVID D. KIRKPATRICK 7 minutes ago
Col. Muammar el-Qaddafi of Libya held control of the capital on Wednesday, but there were indications that the fighting had reached the northwest of the country around Tripoli.

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A Flowering of the Doughnut Arts
By PETE WELLS
A clutch of new shops in New York offers up increasingly outlandish innovations. Dough, in Brooklyn, focuses on clever glazes, including a vivid magenta hibiscus.

- What's Your Ideal Doughnut? | Photos

NEWS ANALYSIS
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OPINION »
Editorial: Spreading Anti-Union Agenda
Republican talk of balancing budgets is cover for the real purpose of gutting the political force of middle-class state workers.
- Friedman: If Not Now, When? | Comments (72)
- Dowd: Black Swan Lakeside
- Bittman: Junk Oatmeal?
- Op-Ed: Turkey Looks East
- Op-Ed: Nepal’s Revolution
- Room for Debate: Another Government Shutdown?
Obesity

- **Body Mass Index (BMI):** A measure of an adult’s weight in relation to his or her height
  - Weight (kg) / Height (cm) $^2$

- **Obesity on an Individual Level:**
  - **Body Mass Index (BMI) ≥ 30**

- **Obesity on a State level:**
  - % of all adults with BMI ≥ 30
Obesity Trends* Among U.S. Adults

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

Source: Behavioral Risk Factor Surveillance System, CDC
Obesity is rarely just about SIZE

- Obesity is related to increased risk for
  - High blood pressure (*hypertension*)
  - Elevated blood sugar levels (*hyperglycemia*)
  - Dysregulated lipoprotein metabolism (*dyslipidemia*):
    - Elevated triglycerides and/or
    - Reduced HDL-cholesterol

- **Metabolic Syndrome (MetS):** 3+ of the above

- **MetS is related to:**
  - Diabetes
  - Cardiovascular Disease
  - Diminished Cognitive Function
MetS & Cognition

• A staggering 34-45% of US adults fulfill criteria for MetS (Ervin, 2009)

• Strong evidence suggests that MetS is harmful to cognition (Kalmijn et al., 2000, Vanhanen et al., 2006, Dik et al., 2007, Yaffe et al., 2007, Gatto et al., 2008, Raffaitin et al., 2009, Yaffe et al., 2009, Akbaraly et al., 2010)
  • The whole is greater than the sum of its parts
  • Little is know about mechanisms

• Knowledge of mechanisms is critical for developing therapeutic interventions

• Prevention is our best defense against late-life cognitive impairment
How can Magnetic Resonance (Brain) Imaging Help?

- A window to the living human brain
  - Biomarkers of disease and disease progression
  - Markers of treatment response
  - Understanding disease pathways
- Safe & non-invasive
  - No radiation
- Contrast agents possible but not necessary
- Good spatial and temporal resolution
- Easy to repeat
- Extremely versatile
MRS

Volume/Atrophy

Chemical Composition

Indirect measure of Brain Activity

MRI

fMRI

many low resolution images (e.g., every 2 sec for 5 mins)
Diffusion Tensor Tractography
fMRI in Clinical Neuroscience

- fMRI has proved extremely useful in identifying abnormal brain function in at-risk individuals (Saykin et al., 1999, Bookheimer et al., 2000, Chang et al., 2001, Sweet et al., 2004, 2006)
  - Increased task-related activation of expected regions
  - Recruitment of additional brain regions
  - Increased task-related de-activation of unexpected brain regions

- Coupled with a well-targeted behavioral challenge, fMRI can unmask early cognitive inefficiencies and compensation

- Coupled with other imaging modalities (e.g., MRS, ASL, vascular ultrasound), we can begin to study the underlying physiological mechanisms
Participants

- Forty right-handed individuals between the ages of 40 and 60
  - 19 MetS (ages 47±6)
  - 21 Healthy Controls (50±5)
- Free of neurological & psychiatric disease
- Ethnically diverse
- Cognitively normal
  - Mean full-scale IQ = 115.0±10.5
  - No significant group differences in age, sex, education or any other cognitive measure
Methods

- General health assessment (height & weight, blood pressure, lipid profile, and fasting glucose)
- Full Neuropsychological Evaluation
- Neuroimaging (Structural, fMRI)

Eight *a priori* Regions of Interest (ROIs)
Results
Conclusions

• fMRI is sensitive to brain changes related to MetS

• Changes may indicate early vulnerability of the fronto-parietal attention/executive system

(why not greater efficiency of processing?!?)

– In younger populations at CVD risk, within the a priori ROIs
  • ↑activation = ↑performance & ↓reaction times for everyone

– In older populations with CVD, within the same ROIs
  • ↓task-related brain activation = ↑large vessel atherosclerosis, ↓endothelial function & clinically significant cognitive impairment
Mechanisms
MetS $\rightarrow$ IS $\rightarrow$ NO $\rightarrow$ BOLD $\rightarrow$ Cog
Insulin Sensitivity & BOLD in obesity

Gonzales et al. (2010), *Obesity*, 18, 2131-2137
Endothelial function & BOLD in middle age

Gonzales et al. (2010), *Brain and Cognition*, 73, 146-151
Future Directions

• Test if the changes are global or specific to cognition and the fronto-parietal network
• Check for evidence of cerebrovascular decoupling
• Validate the alterations as markers of brain vulnerability in longitudinal studies
• Explore the underlying mechanisms by assessing volume, cerebral perfusion and neurochemistry
  – MetS→↓IS→↓plasticity of glutamate receptors→↓Cog
• Test the efficacy of early interventions
Mechanisms
Obesity $\rightarrow$ Neurochemistry $\rightarrow$ Cognitive function
Neurochemical Alterations in Obesity

- General health assessment (height & weight, blood pressure, lipid profile, and fasting glucose)
- Full Neuropsychological Evaluation
- Neuroimaging (Structural, MRS)
Interpretation

- $\uparrow mI$ is associated with cognitive impairment in
  - Down Syndrome
  - Alzheimer’s Disease
  - Mild Cognitive Impairment

- Interpreted as a sign of
  - Gliosis
  - Disturbance in the second messenger signaling involving inositol tri-phosphate
  - Disturbance in fluid homeostasis

- $\uparrow mI$ and abnormal inositol phospholipid metabolism have been reported in diabetes mellitus
Obesity & Cognitive Function

↑ Obesity  ↓ Cognitive Function
Obesity, Dyslipidemia & ml
Future Directions

- Validate the alterations as markers of brain vulnerability in longitudinal studies
- Test the efficacy of early interventions
It is a collaborative effort

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Thank you!
**BOLD signal**

**Blood Oxygen Level Dependent signal**

- neural activity $\Rightarrow$ ↑ blood flow $\Rightarrow$ ↑ oxyhemoglobin $\Rightarrow$ ↑ MR signal

**Basal state**

- normal flow
- basal level [Hbr]
- basal CBV
- normal MRI signal

**Activated state**

- increased flow
- decreased [Hbr] (lower field gradients around vessels)
- increased CBV
- increased MRI signal (from lower field gradients)

Source: fMRIB Brief Introduction to fMRI