Altered Hippocampal Architecture in Alzheimer's Dementia: A Novel Finding on 3 Tesla MRI

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Determining the Location of the Cervicomedullary Junction (Pyramidal Decussation) in Relation to the Obex Using DTI

BACKGROUND

Causes of memory loss
- Normal aging
- Alzheimer’s disease
- Medications
- Depression
- Alcohol
- Head trauma
- Radiation

MEMORY AND AGING

Causes of memory loss

Epidemiology
- About 4 million people in the US
  3-10% of people >65
  About 30% of people >85
  50% to 80% of all Dementia cases

Clinical
- Progressive deterioration of:
  - Cognition
  - Behavior
  - Functionality

MEMORY

A collection of mental abilities that depend on several systems in the brain.

- A memory system is a way in which the brain processes information in order to make it available for use at a later time. Affected differently in normal aging and AD.

Alzheimer’s Disease

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AD genetics
- Causative genes
  - Cause early-onset AD
  - Encode for the proteins:
    - Presenilin 1
    - Presenilin 2
    - Amyloid precursor protein

Susceptibility genes
- Apolipoprotein E
  - Involved in transport and metabolism of lipids
  - 3 isoforms
  - Apo e2 may be protective
  - Apo e3 most common, no increased risk
  - Apo e4
    - 1 copy: 3-4x increased risk of late-onset AD
    - 2 copies: 9-10x increased risk
    - Thought to stabilize the Aβ fibrils
AD Pathophysiology

- Extracellular deposition of β-amyloid
  - Aβ peptide is the main component of amyloid plaques
  - Aβ peptide is neurotoxic
- Intracellular neurofibrillary tangles
  - Formed mainly of tau protein
  - Oxidative neuronal damage
  - Inflammatory cascades

AD

- At autopsy:
  - Brain atrophy
  - Enlarged ventricles

- Biochemistry
  - Deficit in cholinergic system
  - Anticholinesterase inhibitors as therapeutic agents

Neurofibrillary Tangles (Hippocampus: CA1): Tau

Senile (neuritic) plaques

AD pathophysiology

- Imbalance between Aβ production and clearance
- Aβ accumulation leads to misprocessing of tau protein
- Number of amyloid plaques does not correlate well with cognitive impairment
- Found throughout cerebral cortex
- Tau anatomic distribution
  - Entorhinal cortex, amygdala, hippocampus

Progression of Brain Damage in AD

- Entorhinal cortex
- Hippocampus
- Neocortex

Current Role of Imaging in Dementia

- Identify treatable or controllable causes of memory and cognitive impairment.
- Help in diagnosis (together with neuropsychological testing, clinical and laboratory data, genetics markers, etc.)

Standard Imaging Findings in Alzheimer’s Dementia

- Have been validated in large studies of patient’s with cognitive impairment, Alzheimer’s dementia, and other neurodegenerative disorders.
- PROBLEM: Generally only apparent after significant neuronal loss.

Hippocampal Atrophy
Hippocampal Atrophy

Progressive atrophy over time

Decreased Temporoparietal FDG Avidity

Goal of Imaging in Alzheimer’s Dementia
- Early diagnosis which may allow early intervention to preserve brain (neurons, neuropil, connections)

Predicting Progression of MCI to AD
- Rates of Conversion to AD
  - Normal elderly: 1-2% per year
  - MCI: 10-15% per year
  - We would like to identify which MCI patients are going to go on to AD

AREAS OF ACTIVE RESEARCH IN EARLY IDENTIFICATION OF ALZHEIMER’S: SOME MORE PROMISING THAN OTHERS

Amyloid Imaging
- Pittsburgh compound B has been studied the most to date
- Very expensive, requires a cyclotron on site (20 minute half-life of carbon-11)

Sergi G. Costafreda, Ivo D. Dinov, Zhuowen Tu, Yonggang Shi, Cheng-Yi Liu, Iwona Kloszewska, Patrizia Mecocchi...

Automated hippocampal shape analysis predicts the onset of dementia in mild cognitive impairment
NeuroImage Volume 56, Issue 1 2011 212 - 219

Rate of cortical volume loss in MCI
(Kovacec, Raffi, Brewer 2009)
- The more rapid the volume decline, the more likely to develop AD
Segmentation and Thickness Imaging

Limitations of Experimental Approaches

- Most studies to date have been small. Larger studies are needed to validate these findings.
- These findings are useful in classifying patients into various cohorts that can predict risk of AD and cognitive impairment, but are not necessarily predictive in any individual patient.
- Even if validated, these methods are costly, requiring specialized software and very careful data analysis.

An Ideal Early Imaging Test for AD

- Present before significant neuronal loss, allowing early intervention.
- Predictive of cognitive impairment
- Relatively inexpensive – uses conventional neuroimaging and requires no special software
- YOU CAN SEE IT WITH YOUR OWN TWO EYES!

HYPOTHESIS

- Abnormal hippocampal architecture correlates with cognitive impairment in AD.
- Abnormal hippocampal architecture predicts cognitive impairment in AD independent of neuronal loss/atrophy.
- Specific Architecture Change: Loss of lamination of the white matter pathways in the hippocampus.

Imaging the Perforant Pathway

NORMAL HIPPOCAMPUS

LOSS OF WM LAMINATIONS EXAMPLE

Study Design

- Patient selection: Patients evaluated clinically by neurology for memory changes or cognitive impairment who have had a ‘dementia’ protocol MRI on the 3 Tesla Verio magnet.
- Retrospective analysis of approximately 50 consecutive patients imaged between October 2011 and October 2012 (thus far)
- Control: Age and sex matched controls who underwent seizure protocol imaging on the 3 Tesla Verio, excluding those with hippocampal edema from recent seizure.

Study Design

- Imaging: high-resolution T2 imaging to evaluate hippocampal anatomy
- 3 mm T2 coronal slices, FOV 15 x 16 cm, 480 x 512 matrix, TR ~7260/TE ~100/flip angle 150.
- Images scored by 4 radiologists for architectural distortion of hippocampus:
  - 2 attending level, 2 senior (4th year) residents, independently scored and final scored
  - Interpreters blinded as to whether dementia patient (and if dementia, blinded to consensus diagnosis) or normal control.
**Additional Patient Data for Analysis**

- Genetic testing for Apo E4 allele
- Complete neuropsychological testing

**RESULTS**

- STAY TUNED
- STUDY PROPOSAL SUBMITTED FOR IRB APPROVAL (PENDING)

**ADDITIONAL REFERENCES**