RELATING BEHAVIOUR AND STRUCTURAL CONNECTIVITY IN ALZHEIMER’S DISEASE AND MILD COGNITIVE IMPAIRMENT

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BIC Lecture Series
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Outline

• Introduction
  • Alzheimer’s disease (AD), mild cognitive impairment (MCI)
  • AD propagates along networks
  • The ADNI dataset

• Morphometry
  • Methods – cortical thickness
  • Morphometric changes in AD and MCI
  • Relating morphometry to behaviour

• Network analysis
  • The methods – graph theory 101
  • Connectivity changes in AD and MCI
  • Relating connectivity to behaviour

• Summary
  • What have I found, and what’s next?
Introduction

• Alzheimer’s disease (AD)
  • First characterized by Alois Alzheimer (1906)
  • Senile/neuritic plaques – amyloid-β (Aβ)
  • Neurofibrillary tangles – hyperphosphorylated tau
  • Originates in entorhinal cortex, hippocampus
  • Early onset (rare): 40s & 50s, fast progression, strong genetic component
  • Late onset (common): 60+ (13%), 85+ (45%), gradual progression
  • 60-80% of all dementias
  • About twice as likely for females than males
  • Today – 500,000 Canadians with dementia; projection for 2038 – 1,000,000

Sources: www.alz.org, www.alzheimer.ca
Introduction

• Mild cognitive impairment (MCI)
  • Putative “prodromal” risk state for AD
  • Mild (measurable) memory, language, executive impairment
  • Doesn’t interfere with daily activities
  • Conversion to AD – 10-15% per year
  • Umbrella term, amnesic MCI has a higher associated risk
Introduction

The clinical use of structural MRI in Alzheimer disease

Giovanni B. Frisoni, Nick C. Fox, Clifford R. Jack Jr, Philip Scheltens and Paul M. Thompson

Abstract | Structural imaging based on magnetic resonance is an integral part of the clinical assessment of patients with suspected Alzheimer dementia. Prospective data on the natural history of change in structural markers from preclinical to overt stages of Alzheimer disease are radically changing how the disease is conceptualized, and will influence its future diagnosis and treatment. Atrophy of medial temporal structures is now considered to be a valid diagnostic marker at the mild cognitive impairment stage. Structural imaging is also included in diagnostic criteria for the most prevalent non-Alzheimer dementias, reflecting its value in differential diagnosis. In addition, rates of whole-brain and hippocampal atrophy are sensitive markers of neurodegeneration, and are increasingly used as outcome measures in trials of potentially disease-modifying therapies. Large multicenter studies are currently investigating the value of other imaging and nonimaging markers as adjuncts to clinical assessment in diagnosis and monitoring of progression. The utility of structural imaging and other markers will be increased by standardization of acquisition and analysis methods, and by development of robust algorithms for automated assessment.

Introduction

- Propagation of AD pathology
  - Originates in entorhinal cortex (Braak stages I and II)
  - Spreads to hippocampus and amygdala (Braak stages III and IV)
  - Remainder of cortex (T>P>F>O) & subcortex (Braak stages V and VI)
  - Dementia highly related to synaptic degeneration
  - Probable activity-dependent component (LTP, LTD) – epilepsy
  - Physical transsynaptic spread also demonstrated:

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Transsynaptic Progression of Amyloid-β-Induced Neuronal Dysfunction within the Entorhinal-Hippocampal Network

Julie A. Harris,1,2 Nino Devidze,1 Laure Verret,1,2 Kaitlyn Ho,1 Brian Halabisky,1,2 Myo T. Thwin,1 Daniel Kim,1 Patricia Hamto,1 Iris Lo,1 Gui-Qiu Yu,1 Jorne J. Palop,1,2 Eliezer Masliah,3,4 and Lennart Mucke1,2,*

Neuron 68, 428–441, November 4, 2010

Trans-Synaptic Spread of Tau Pathology In Vivo

Li Liu1, Valerie Drouet1, Jessica W. Wu1, Menno P. Witter2, Scott A. Small3, Catherine Clelland1, Karen Duff1,4*

Introduction

A. Rat network

B. Primate network

C. Synapses

D. Microcircuits

Source: Reid & Evans, submitted
Introduction

Cortical Hubs Revealed by Intrinsic Functional Connectivity: Mapping, Assessment of Stability, and Relation to Alzheimer’s Disease


The Journal of Neuroscience, February 11, 2009 • 29(6):1860–1873
Introduction – Major questions

• How is cortical morphometry (e.g., cortical thickness) affected by AD and MCI?
• Do CT changes follow known network structure (e.g. default mode network)?
• What can CT correlations tell us about AD-related changes?
  • Do they predict clinical diagnoses?
  • Do they predict behavioural outcomes?
• How do they relate to functional correlations (fMRI, FDG-PET?)
Introduction – The ADNI Dataset

- Large dataset (800 subjects) – Normal, MCI, AD groups
- Publicly available
- Multicentre (U.S., Canada)
- Longitudinal (6, 12, 18, 24 mo.)
- Multimodal imaging (T1, FDG, PiB-PET)
- Multiple behavioural measures
- Blood samples
- Genetics – including many whole genome sequences
- ADNI2: fMRI, DWI, etc.

Source: www.adni-info.org
Morphometry – Civet Pipeline

original image → template image → normalized image → surface extraction

masking & skull stripping → tissue classification → cortical thickness estimation
Morphometry – Statistical Analysis

- Surface coregistration of all subjects to an iterative population average template surface
- Vertex-wise general linear models = 80,924 analyses
- Family-wise error correction with random field theory (RFT)

An unbiased iterative group registration template for cortical surface analysis
Oliver Lyttelton, Maxime Boucher, Steven Robbins, and Alan Evans*

www.elsevier.com/locate/ynimng
NeuroImage 34 (2007) 1535 – 1544
Cortical thickness – Clinical Assessments

Normal-MCI

MCI-AD

Normal-AD

MMSE

0.0  0.4mm

0.0  0.4mm

0.0  0.4mm

0.0  0.03
Cortical thickness – ADAS-cog

- Alzheimer’s Disease Assessment Scale – cognitive subscale
- Score of 1-70 (higher = more dysfunction)
- Various cognitive tasks, including language, recall, orientation, etc.
- Variance across normal and clinical population; less ceiling effect than MMSE
Cortical thickness – BNT

- Boston Naming Test
- Confrontational naming task
- Measure of anomia
- Identification of drawings, low- to high-frequency words
- Scored from 1-30 (higher=better performance)
Cortical thickness – NPI-Q

- Neuropsychiatric Inventory Questionnaire
- Neuropsychiatric symptoms, including: hallucinations, aggression, anxiety, depression, apathy, euphoria, etc.
- Scored by frequency and severity of symptoms, and caregiver distress
- 0 to 15, higher = more severe
Summary – Morphometry

• Clinical group, MMSE, and ADAS-cog have remarkably similar patterns – highest cortical thinning in known hub regions (see Buckner et al.)

• Substantial atrophy occurs between NC and MCI (i.e., concurrent with cognitive decline)

• Anomia (BNT) associates with thinning in lateral, inferior, and medial temporal lobe; to a lesser extent, angular gyrus, medial and dorsolateral frontal, posterior cingulate/precuneus

• Severity of psychiatric symptoms (NPIQ) less strong, focused on anterior cingulate, prefrontal, lateral temporal, and parahippocampal
Network Analysis – Graph Theory 101

Graph:
Set of vertices (sing. vertex) connected by a set of edges; abstract representation of a network.

Degree:
Total number of edges joining a vertex to other vertices (how many neighbours does it have?)

Sparsity:
Total number of edges $N$ in the graph $G$, as a ratio of all possible edges:
$$s = 1 - \frac{N_G}{N_{ideal}}$$
Network Analysis – Efficiency

Shortest path length $d_{ij}$:
Minimal number of edges required to reach vertex $i$ from vertex $j$.
Here, $d_{ij} = 3$ (note that two possible shortest paths exist).

Clustering coef. $cc_i$:
Number of edges between the neighbours of vertex $i$, as a ratio of all possible edges. Here:
$$cc_i = 3 / 6 = 0.5$$

Global efficiency $E_{\text{glob}}$:
Average inverse shortest path length over $G$, as ratio of ideal $E(G)$:
$$E(G) = \frac{1}{N(N-1)} \sum_{i \neq j \in G} \frac{1}{d_{ij}}.$$  
$$E_{\text{glob}} = \frac{E(G)}{E(G_{\text{ideal}})}.$$  

Local efficiency $E_{\text{loc}}$:
Average $E(G_i)$ as a ratio of the ideal $E(G_i)$, where $G_i$ is vertex $i$'s local neighbourhood:
$$E_{\text{loc}} = \frac{1}{N} \sum_{i \in G} \frac{E(G_i)}{E(G_i^{\text{ideal}})}.$$  

Network Analysis – Centrality

Degree centrality:
Simply, the degree of each vertex. Can optionally be normalized to the maximal degree (N-1).

Betweenness centrality:
The frequency with which vertex i occurs in shortest paths between all other pairs of vertices. Two examples are illustrated.
Network Analysis – Correlative network

AAL parcellation (76 cortical ROIs)

ROI-wise correlations (mean CT values)

Correlation matrix (FDR corrected)

$r = 0.6$
Network Analysis – Sparsity threshold
Network Analysis – Bootstrapping

- Randomly sample from the data, with replacement
- Obtain measures for each sample; use resulting distribution for statistical comparisons
Efficiency – Clinical Groups

Pearson Correlations by Group (uncorrected)

Global Efficiency

Local Efficiency

Integrated Global Efficiency

Integrated Local Efficiency
Efficiency – ADAS-cog

Pearson Correlations by ADAS-cog Group (uncorrected)

Global Efficiency

Local Efficiency

Integrated Global Efficiency

Integrated Local Efficiency
Betweenness Centrality – ADAS-cog

Betweenness centrality, sorted by ADAS low

Betweenness centrality, sorted by ADAS mid

Betweenness centrality, sorted by ADAS high
Efficiency – Boston Naming Test (BNT)

Pearson Correlations by BNT Group (uncorrected)

Global Efficiency

Local Efficiency

Integrated Global Efficiency

Integrated Local Efficiency

BNT high (29-30)  BNT mid (25-28)  BNT low (0-24)
Betweenness Centrality – BNT
Efficiency – Neuropsychiatric Inventory Q

Pearson Correlations by NPIQ Group (uncorrected)

Global Efficiency

Local Efficiency

Integrated Global Efficiency

Integrated Local Efficiency
Betweenness Centrality – NPIQ
Summary – Network Analyses

• Both clinical diagnosis and ADAS-cog score result in networks with increased global efficiency; and an increase, then decrease in local efficiency – networks becoming more “random”, less robust (c.f. He et al., 2008)?
• BNT & NPIQ patterns differ from dementia ratings and from each other – correlations reflecting coordinated atrophy?
• ROI-wise changes in centrality: highlight a substantial reorganization of the network structure; hubs may indicate which ROIs are most vulnerable to degeneration, depending on the severity of behavioural deficits
• Necessary to evaluate local patterns, rather than global alone
Interpretation

- How do we interpret a correlation?
  - Mutually trophic influences on neural growth between connected regions – evidence from animal studies
  - Could also be common afferents, or common modulatory influences
  - Genetic patterns – evidence for this also
  - Coordinated atrophy – particularly relevant for degenerative processes

- Multimodal comparison
  - How do correlations compare to existing knowledge of anatomy (e.g., from rhesus macaques)?
  - How do they compare to functional correlations (fMRI, FDG-PET)?
  - How do they compare to DWI evidence for WM morphometry?
Interpretation – CT vs. DWI networks

Convergence and divergence of thickness correlations with diffusion connections across the human cerebral cortex

Gaolang Gong a,b, Yong He a, Zhang J. Chen b, Alan C. Evans b,*

NeuroImage 59 (2012) 1239–1248

Source: Gong et al, Neuroimage, 2012
Interpretation – Multimodal comparison

- Collations of Connectivity Data on the Macaque brain
- ~500 tract tracing articles
- Regional Map (Kötter & Wanke, 2005) – homology across primate species

Source: Reid et al., preliminary
Interpretation – Multimodal comparison

- Collations of Connectivity Data on the Macaque brain
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<table>
<thead>
<tr>
<th></th>
<th>CT Correlative</th>
<th>CoCoMac</th>
<th>DWI</th>
</tr>
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<tbody>
<tr>
<td>Accuracy</td>
<td>0.58</td>
<td>0.62</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Source: Reid et al., preliminary
Interpretation – Multimodal comparison

- Collations of Connectivity Data on the Macaque brain
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Source: Reid et al., preliminary
What’s next?

• Develop a methodology for treating continuous variables as continuous, rather than as groups: massive linear model with interaction terms.
• Computation models of growth assumptions (i.e., “mutually trophic influences”)
• Application of graph methodology to the prediction of behavioural change based upon T1 imaging; or as a surrogate clinical endpoint
• Comparison with other modalities and characterization of similarities/differences – inference about the biological mechanisms of morphological correlations
Thank you!

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