Tau, Aβ and network degeneration in Alzheimer’s disease

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Congratulations Professor Aguzzi!
Content

1. Network model of neurodegeneration
2. AT(N) in Alzheimer’s disease
3. Spread of Amyloid-β pathology
4. Spread of Tau pathology
5. Interplay between Amyloid-β and Tau pathology
6. Amyloid-β and Tau vs Neurodegeneration
7. Future applications of network models

→ All based on PET and MRI studies in living humans!
1. Network model of neurodegeneration

Seeley et al. (2009) Neuron
2. AT(N): Towards a biological definition of AD

<table>
<thead>
<tr>
<th>ATN profiles</th>
<th>Biomarker category</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-T-N-</td>
<td>Normal AD biomarkers</td>
</tr>
<tr>
<td>A+T-N-</td>
<td>Alzheimers pathophysiology</td>
</tr>
<tr>
<td>A+T-N+</td>
<td>Alzheimers disease</td>
</tr>
<tr>
<td>A+T+N-N</td>
<td>Non-AD pathophysiology</td>
</tr>
<tr>
<td>A+T+N+</td>
<td>Non-AD pathophysiology</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Biomarker Profile</th>
<th>Syndromal Cognitive Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cognitively unimpaired</td>
</tr>
<tr>
<td>A⁻ T⁻ (N⁻)</td>
<td>normal AD biomarkers, cognitively unimpaired</td>
</tr>
<tr>
<td>A⁺ T⁻ (N⁻)</td>
<td>Preclinical Alzheimer’s pathologic change</td>
</tr>
<tr>
<td>A⁺ T⁺ (N⁻)</td>
<td>Alzheimer’s and concomitant suspected non Alzheimer’s pathologic change, cognitively unimpaired</td>
</tr>
<tr>
<td>A⁺ T⁺ (N⁺)</td>
<td>Preclinical Alzheimer’s disease</td>
</tr>
</tbody>
</table>

3. Spread of amyloid-β pathology

- Aβ PET
- Default mode network
- Hub regions
- Aerobic glycolysis

Amyloid-β pathology: PET vs CSF

Higher frequency of CSF+/PET- vs CSF-/PET+ → CSF becomes abnormal before PET?

Discordant in 10-20% of cases

Mattsson et al. (2015) *Brain*
Earliest Aβ PET changes are observed in default mode network regions and other multimodal association areas.
4. Spread of Tau pathology

Xia et al. Alz & Dementia (2013)
Chien et al. JAD (2013)
## Imaging application of NFT Braak staging

<table>
<thead>
<tr>
<th>Braak 1</th>
<th>Entorhinal cortex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Braak 2</td>
<td>Hippocampus</td>
</tr>
<tr>
<td>Braak 3</td>
<td>Parahippocampal gyrus, Lingual gyrus, Amygdala</td>
</tr>
<tr>
<td>Braak 4</td>
<td>Inferior temporal, Middle temporal, Temporal pole, Thalamus, Caudal/rostral/posterior cingulate, Insula</td>
</tr>
<tr>
<td>Braak 5</td>
<td>Frontal, Parietal, Occipital, Transverse, Sup Temporal &amp; banks, Precuneus, Caudate nucleus, Putamen</td>
</tr>
<tr>
<td>Braak 6</td>
<td>Post-, Pre- and Paracentral gyrus, Cuneus, Pericalcarine</td>
</tr>
</tbody>
</table>
Longitudinal Tau PET

1. Highest rates of tau accumulation in AD vs controls
2. Subtly more tau accumulation in Aβ+ vs Aβ- controls

Annual change in tau PET signal:
1. 0-2% in Aβ+ controls
2. 3-8% in symptomatic AD

Harrison et al. 2019 Annals of Neurology
Pontecorvo et al. 2019 Brain
Cho et al. 2019 JNM

1. Jack et al. 2018 Brain
AD01
AD02
AD....
AD36

SUVr Seed region

COVARIANCE MAP

1 SUVr target voxel 10
Network spread of tau pathology?

- Tau PET covariance in AD 63 patients
- Functional connectivity in 1,000 young adults

Visual network seed

- Executive control network seed
- Default mode network seed

Ossenkoppele et al. (2019) NeuroImage Clinical
Network spread specific to tau pathology?

Stronger network spread for tau compared to Aβ
Functional connectivity brain architecture predicts the rate of tau accumulation

\[ \beta = 0.38, p<0.001 \]
5. Interplay between Amyloid-β and Tau pathology

Van der Kant, Goldstein & Ossenkoppele (2019) Nature Reviews Neuroscience
Evidence supporting Amyloid-β cascade model

Tau positivity almost exclusively occurs in Amyloid-positive persons (+ higher rates of tau accumulation)

Ossenkoppele et al. (2018) JAMA
Higher tau PET signal 5 years later in CSF+/PET+ vs all other groups

Of the 34 Amyloid-β CSF+/PET- subjects:
- 11 (32%) turned Amyloid-β PET+
- Only 1 (3%) turned Tau PET+

CSF Aβ+ → PET Aβ+ → PET Tau+

“It takes two to tangle”

Reimand et al.Submitted
Spatial paradox

Primary age-related tauopathy (PART)

Van der Kant, Goldstein & Ossenkoppele (2019) Nature Reviews Neuroscience
Neurogenetic contributions to tau and Aβ spread

Tau propagation pattern

Spatial overlap with gene expression from the AHBA

Aβ propagation pattern


Genetic interactions
Beyond cortical associations

Gene expression–neuroimaging
Cortical association

Interactome
Lipid metabolism
APOE

Shared genetic expression
MapT + 353
CLU + 215
Amyloid related
Amyloid imaging

Genetic vulnerability toward a combined phenotype

Phenotype (neuroimaging)

Genotype and gene expression

2% >3.5 s.d. 96%
Connectivity score (z-score)

2% >3.4 s.d. 98%
Connectivity score (z-score)
Clinical trial of Aβ clearance strategy resulting in decreased amyloid plaque burden

MCI due to AD

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>Placebo</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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</thead>
<tbody>
<tr>
<td>Tau pathology</td>
<td>↓ Tau pathology</td>
<td>↓ Tau pathology</td>
<td>↑ Tau pathology</td>
<td>↑ Tau pathology</td>
<td></td>
</tr>
<tr>
<td>Neurodegeneration</td>
<td>↓ Neurodegeneration</td>
<td>↑ Neurodegeneration</td>
<td>↓ Neurodegeneration</td>
<td>↑ Neurodegeneration</td>
<td></td>
</tr>
<tr>
<td>Cognitive function</td>
<td>↓ Cognitive function</td>
<td>↑ Cognitive function</td>
<td>↓ Cognitive function</td>
<td>↑ Cognitive function</td>
<td></td>
</tr>
<tr>
<td>✓ Tau pathology is Aβ driven</td>
<td>✓ Tau pathology is Aβ driven</td>
<td>× Tau pathology is Aβ driven</td>
<td>✓ Tau pathology is Aβ driven</td>
<td>× Tau pathology is Aβ driven</td>
<td></td>
</tr>
<tr>
<td>✓ AD treatment</td>
<td>× AD treatment</td>
<td>✓ AD treatment</td>
<td>× AD treatment</td>
<td>✓ AD treatment</td>
<td></td>
</tr>
</tbody>
</table>

18 months

Van der Kant, Goldstein & Ossenkoppele (2019) Nature Reviews Neuroscience
EMERGE and ENGAGE: Composite SUVR change from baseline

**Medial temporal composite**

- Placebo: n=11
- Low dose: n=14
- High dose: n=11

HIPPOCAMPUS
PARAHIPPOCAMPAL
TEMPORAL LOBE ANTERIOR MEDIAL
(includes Entorhinal and Amygdala)
TEMPORAL LOBE ANTERIOR LATERAL

**Temporal composite**

- Placebo: n=11
- Low dose: n=14
- High dose: n=11

TEMPORAL LOBE Comprised of:
SUPERIOR, POSTERIOR, MIDDLE INFERIOR
POSTERIOR, SUPERIOR ANTERIOR,
FUSIFORM GYRUS

**Frontal composite**

- Placebo: n=11
- Low dose: n=14
- High dose: n=11

FRONTAL LOBE Comprised of:
MIDDLE, PRECENTRAL, STRAIGHT GYRUS
INFERIOR, SUPERIOR
ORBITOFRONTAL CORTEX Comprised of:
ANTERIOR, MEDIAL, LATERAL, POSTERIOR
Patients with PCA (the “visual variant of AD”)

Amyloid PET using \(^{[11}C\)PIB:

Tau PET using \(^{[18}F\)AV-1451:

Ossenkoppele et al. Brain (2016)
Tau, but not Aβ, mirrors the pattern of neurodegeneration


Tau pathology exceeds FDG pattern, predicts future hypometabolism?
Patients
32 patients with clinical AD and positive PIB-PET scan

Does tau PET elevation precede and predict future atrophy? (severity and topography)

Aβ-PET, tau-PET and future atrophy

The intensity of tau-PET (not amyloid) binding at baseline predicts the severity of subsequent atrophy.
Conclusions

• Early multifocal Aβ PET changes in multimodal association areas
• Tau PET signal spreads connectivity based from initial epicenter
• Neocortical tau PET signal almost exclusively observed in Aβ+ persons
• Degree of Aβ dependence for tau PET spread is largely unknown
• Tau (> than Aβ) is intimately linked to neurodegeneration

→ Peak into the future
**METHODS**

Voxelwise "spatial" correlations

**GROUP LEVEL**

Baseline FTP to atrophy
Mean Z(r) = 0.780
→ 43% shared variance

Baseline PIB to atrophy
Mean Z(r) = 0.183
→ 3% shared variance

**INDIVIDUAL PATIENT**

At the individual level, baseline FTP pattern predicts the pattern of subsequent atrophy
Tau-PET and future atrophy

Patient #1
CDR 1, CDR-SB 4.5, MMSE 27

Patient #2
CDR 1, CDR-SB 4.5, MMSE 28
Connectivity-Based Forecasts of Spreading Brain Atrophy

Behavioral variant FTD

Semantic variant PPA

Brown et al. (2019) Neuron
Oskar Hansson  
Niklas Mattsson  
Sebastian Palmqvist  
Ruben Smith  
Shorena Janelidze  
Philip Insel  
Olof Strandberg  
David Berron  
Antoine Leuzy  
Jonas Jester-Broms  
Daniëlle van Westen

Philip Scheltens  
Wiesje van der Flier  
Yolande Pijnenburg  
Pieter Jelle Visser  
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Niels Prins  
Frederik Barkhof  
Bart van Berckel  
Ronald Boellaard  
Sandeep Golla  
Anita van Loenhoud  
Tessa Timmers  
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Bill Seeley  
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Michel Grothe  
Sylvia Villeneuve  
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Paul Crane  
Amyloid Biomarker Study Group  
BEAT-IT Study Group