Imaging the molecular pathology of inflammation and tau in dementia

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Disclosures

Professor John O’Brien serves as a consultant to Avid/ Lilly, GE Healthcare, TauRx and Axon

He will be discussing the research use of AV1451 as a tau PET ligand. AV1451 is not a clinically approved ligand
Brain imaging in dementia

• Rule out other brain disorders
• Assist with subtype diagnosis
• Stratify subjects for clinical trials/ treatments
• Outcome biomarker for clinical trials
• Investigate underlying neurobiology and mechanisms
Causes of Alzheimer’s disease: the amyloid cascade hypothesis

Environment and Genetic variation

Amyloid (plaques) → Tau (tangles) → Neuronal cell loss → Neurotransmitter changes → Dementia
Causes of Alzheimer’s disease: the amyloid cascade hypothesis

- Amyloid (plaques)
- Tau (tangles)
- Inflammation
- Environment and Genetic variation
- Neuronal cell loss
- Neurotransmitter changes
- Dementia
Neuroinflammation: a key mechanism in Alzheimer’s and other dementias?

- Long term use of anti-inflammatories appears protective against AD/dementia
- GWAS studies strongly implicate inflammatory mechanisms in AD aetiology (e.g. TREM2, CD33)
- Microglial activation occurs in AD and other dementias (in animal models and in vivo)
- Renewed interest in therapeutic studies targeting this pathway
- However, timing and impact of inflammatory changes unclear and precise mechanisms not defined
Systemic inflammation and disease progression in Alzheimer disease

**Graph 1:**
- **X-axis:** Time of follow-up (months)
- **Y-axis:** Mean change in ADAS-Cog score from baseline (SE)
- **Legend:**
  - SIE absent
  - SIE present

**Table:**

<table>
<thead>
<tr>
<th>Time Period</th>
<th>SIE Absent (n)</th>
<th>SIE Present (n)</th>
<th>t test p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2 months</td>
<td>162</td>
<td>60</td>
<td>0.5</td>
</tr>
<tr>
<td>0-4 months</td>
<td>127</td>
<td>95</td>
<td>0.04</td>
</tr>
<tr>
<td>0-6 months</td>
<td>112</td>
<td>110</td>
<td>0.04</td>
</tr>
</tbody>
</table>

**Graph 2:**
- **X-axis:** TNF-α levels
- **Y-axis:** Mean change in ADAS-Cog score from baseline (SE)
- **Legend:**
  - Low TNF-α
  - High TNF-α

**Notes:**
- Low TNF-α: SIE absent (n=31), SIE present (n=28)
- High TNF-α: SIE absent (n=81), SIE present (n=82)
Relationship between AD biomarkers in the DIAN study

Inflammation?
Serial MR Imaging in AD and DLB

Mak et al, Neuroimage Clinical, 2015

R = 0.49, p < 0.01
Pittsburgh compound B imaging for amyloid

PIB positive

PIB negative
Amyloid PET imaging

Negative scan: normal

Positive scan: amyloid

Flurbetapir (Amyvid)
Flurbetaben (NeuraCeq)
Flutametamol (Vizamyl)
Amyloid β deposition and cognitive decline in Alzheimer’s disease: a prospective cohort study

Villemagne et al, Lancet Neurol, 2013
Challenges of imaging inflammation in the brain

- Most PET ligands based on TSPO (Translocator protein) which is a marker of microglial activation
- TSPO is phylogenetically conserved receptor on mitochondrial membrane
- Does not capture astrocytosis
- PK11195 best studied tracer, but sensitivity may be suboptimal
- Other tracers (PBR28) may be more sensitive, but genetic polymorphisms (TSPO rs6971) affect binding, with 40% population being low binders

Stephaniak and O’Brien, 2016
Imaging of neuroinflammation in dementia: a review

James Stefaniak, John O’Brien

- 28 published studies in MCI or dementia, 19 of which used PK11195
- 25 studies in AD, one each in DLB, PDD, FTD, none in late life depression
- Of 17 studies reporting AD v Control comparison, 11 found increase in AD, 6 no difference
- Of 8 studies in MCI, 5 found no increase
- Small, cross-sectional, most didn’t include other measures (amyloid, tau, peripheral markers)
Increased PK 11195 binging in anterior cingulate in late life depression (case series)

Su et al, 2016
PK11195 PET imaging in AD, PSP, FTD, DLB: Cambridge NIMROD Study

Mild AD/ Prodromal, Mean MMSE 25.4

Passamonti et al, 2018
Inflammation (PK11195) in a 53yo presymptomatic MAPT mutation carrier

Bevan-Jones et al, in press
Several tau tracers available and more in development

- THK family
- PBB3
- AV 1451 ("Flortaucipir")
- MD-6240
- Roche
- Genentec

Still require careful validation (some off target binding)
Tau isoforms in humans

AD (mixed 3 and 4 repeat; PHF)

PSP (4 repeat; straight)

Luc Bluee et al, 2010; Goedert et al, 2018
Tau deposition (AV 1451), unlike amyloid PET, mirrors clinical phenotype in AD

Tau much more strongly associated with structural atrophy than amyloid
AD and the FTD spectrum

From BAP Dementia Guidelines: O’Brien et al, 2017
Neuroimaging of Inflammation in Memory and Other Related Disorders (NIMROD) study

<table>
<thead>
<tr>
<th></th>
<th>AD/MCI+ (n = 15)</th>
<th>PSP (n = 19)</th>
<th>Healthy controls (n = 13)</th>
<th>Group difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>9/6</td>
<td>11/8</td>
<td>6/7</td>
<td>N/S</td>
</tr>
<tr>
<td>Age, years (SD, range)</td>
<td>71.6 (± 8.7, 54–85)</td>
<td>69.5 (± 5.8, 52–79)</td>
<td>67.2 (± 7.3, 55–80)</td>
<td>F = 1.2, P = 0.3</td>
</tr>
<tr>
<td>Education, years (SD, range)</td>
<td>14.3 (± 3.3, 10–19)</td>
<td>11.9 (± 1.8, 10–17)</td>
<td>15.8 (± 1.9, 11–19)</td>
<td>F = 10.2, P = 0.0003</td>
</tr>
<tr>
<td>MMSE (SD, range)</td>
<td>25.5 (± 2.8, 18–28)</td>
<td>26.1 (± 4.5, 13–30)</td>
<td>29.3 (± 0.7, 28–30)</td>
<td>F = 4.9, P = 0.012</td>
</tr>
<tr>
<td>ACE-R (SD, range)</td>
<td>75.9 (± 11.0, 51–89)</td>
<td>78.7 (± 15.8, 36–95)</td>
<td>95.5 (± 3.0, 89–99)</td>
<td>F = 10.3, P = 0.0002</td>
</tr>
<tr>
<td>PSP Rating Scale (SD, range)</td>
<td>–</td>
<td>43.6 (± 15.8, 15–74)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Values are mean (±SD, range).
AD/MCI+ = Alzheimer’s disease/mild cognitive impairment (amyloid-positive from PiB-PET scan); MMSE = Mini-Mental State Examination; ACE-R = Addenbrookes’ Cognitive Examination, Revised. N/S = not significant at P < 0.05 (uncorrected).

AD/MCI+ = 9 subjects with probable AD and 6 with PiB +ve MCI

PSP = Progressive Supranuclear Palsy
Methods

• 370 MBq AV1451 injected

• Scanning on GE PET, dynamic imaging over 90 minutes (58 frames)

• Non-displaceable binding potential (BPND) determined for each region on Hammers atlas using simplified reference (cerebellar grey matter) tissue model (SRTM)

• Results corrected for partial volume (CSF), but similar results obtained from uncorrected data
[Image of a bar graph showing comparisons between AD/MCI+, PSP, and HC groups across various brain regions and imaging metrics. The graph illustrates differences in brain region activity or metabolism between the groups.].
Alzheimer’s disease (n = 15)

Progressive supranuclear palsy (n = 19)

Healthy Controls (n = 13)
 Tau imaging with AV1451 in AD and PSP

Clearly differentiates AD from PSP with differences in keeping with known and distinct regional distributions

Passamonti, Vázquez Rodríguez et al, Brain 2017
Longitudinal Assessment of Tau Pathology in Patients with Alzheimer’s Disease Using $[^{18}\text{F}]$ THK-5117 Positron Emission Tomography

Ishiki et al, 2015
• Found much less AV1451 binding than in AD

• Still sig increase c/w controls

• Pattern of binding in DLB different from AD (occipital increases)
Comparing $^{18}$F-AV-1451 with CSF t-tau and p-tau for diagnosis of Alzheimer disease

- 30 controls, 15 prodromal AD, 39 AD dementia
- Tau (AV1451) PET, MRI, CSF biomarkers assessed

Mattson et al, Neurology, 2018; also Ossenkoppele et al, 2018

![Graphs showing sensitivity and specificity for different biomarkers in AD and control groups.](image)

Tau PET sig better in AD dementia than other markers
AD and the FTD spectrum

From BAP Dementia Guidelines: O’Brien et al, 2017
Post-mortem validation of AV1451

Suggests strong binding to paired helical filament tau in AD

No binding to TDP-43.

Promising in vivo ligand for differentiating AD from TDP-43 FTD

Marquie et al, 2015
AV1415 binding also increased in vivo in Semantic dementia (TDP-43 pathology).

7 cases of Semantic Dementia

4 had AD biomarkers: one negative PiB PET scan, three others had total tau and ratio levels not in AD range.
Flortaucipir tau PET imaging in semantic variant primary progressive aphasia

Sara J Makaretz, Megan Quimby, Jessica Collins, Nikos Makris, Scott McGinnis, Aaron Schultz, Neil Vasdev, Keith A Johnson, Bradford C Dickerson
AV 1451 binding in a C9orf72 mutation (assoc with TDP-43 pathology)

Bevan-Jones et al, 2018
• Central inflammation can be detected in early/prodromal AD and correlates with disease severity; also occurs in early (pre-symptomatic) FTD

• Such information key to timing of therapeutic interventions

• Tau imaging developing, sensitive for tau (AD, PSP, DLB) but some issues with specificity (TDP-43)

• Tau markers correlate more strongly with clinical profile, progression and structural atrophy than amyloid

• Markers for tau and inflammation need further development
Can imaging determine whether prion like spread of tau and other proteins occurs?

REVIEW ARTICLE

Like prions: the propagation of aggregated tau and α-synuclein in neurodegeneration

Michel Goedert, Masami Masuda-Suzukake and Benjamin Falcon
Tau burden and the functional connectome in Alzheimer’s disease and progressive supranuclear palsy

Does tau spread through the brain in humans and if so how?
Why are some brain areas more affected by tau?

• In many degenerative disorders, highly connected areas (hubs) are the most prone to neurodegeneration/atrophy.

• Three main hypotheses as to why these “hubs” vulnerable:

  1. Pathology spreads through the brain trans-neuronally in prion-like way

  2. Hubs selectively vulnerable because of high metabolic demands

  3. Hubs selectively vulnerable because of lack trophic support/ differential gene expression/ other factors

Cope et al, Brain, 2018
Can this be tested using graph theory metrics?

Cope et al, Brain, 2018
Graph Metrics: to investigate spread tau

Anchorage
low clustering

Lima
high participation

Beijing
high degree
Can this be tested using graph theory metrics?

- Assoc with trophic support
- Assoc with metabolic demand
- Number and strength of connections to other hubs

Clustering
 Participation
 Degree

Cope et al, Brain, 2018
Different hypotheses predict different results

1. Pathology spreads through the brain trans-neuronally in prion like way. Predicts higher tau burden in nodes with higher “weighted degree”

2. Hubs selectively vulnerable because of high metabolic demands. Predicts higher tau burden in nodes with higher “participation co-efficient”

3. Hubs selectively vulnerable because of lack trophic support/ differential gene expression/ other factors. Predicts negative relationship between tau and “clustering co-efficient”

Cope et al, Brain, 2018
Methods

• AV1451 tau PET (as before)

• 3T Resting state BOLD (11 minutes, multi-echo)

• Harvard-Oxford atlas used, brain parcellated into 598 regions of equal size

• BOLD time series extracted for each region

• Graph theory analysis (Maybrain software) to assess metrics including weighted degree, participation co-efficient, clustering co-efficient

Cope et al, Brain, 2018
Significant association between AV binding and weighted degree

R=0.48, p<0.0001
Significant inverse association between AV binding and weighted participation co-efficient

No sig association with Clustering coefficient

R=0.30, p<0.0001

Cope et al, Brain, 2018
Results in AD consistent with:

1. Pathology spreads through the brain trans-neuronally in prion like way. Predicts higher tau burden in nodes with higher “weighted degree”

2. Hubs selectively vulnerable because of high metabolic demands. Predicts higher tau burden in nodes with higher “participation co-efficient”

3. Hubs selectively vulnerable because of lack trophic support/ differential gene expression/ other factors. Predicts negative relationship between tau and “clustering co-efficient”

Cope et al, Brain, 2018
• Multi-modal analysis using graph theory consistent with “prion like” spread of tau pathology in AD
• Caution needed as cross-sectional data used
• Illustrates potential power of multi-modal imaging data to investigate neurobiology in vivo
• Further longitudinal studies needed