AABC Webinar

Updates in Neuroimaging

12/9/19

Make sure you have a solid internet connection.
Use a headset/earbuds for the best audio experience.

Please ask questions by typing them in on the bottom of the screen at “Q&A”.
Q&A will be 5:50 p.m.
Michael Ewers, PhD
michael.Ewers@med.uni-muenchen.de
*Functional Connectomics to Predict Tau Spreading and Cognitive Resilience in Alzheimer’s disease*

Beau Ances, MD, PhD, MSc
bances@wustl.edu
*Neuroimaging Insights from the Dominantly Inherited Alzheimer’s Network (DIAN)*

Liana Apostolova, MD, MSc, FAAN
lapostol@iu.edu
*Improving our understanding of Alzheimer’s disease heterogeneity: LEADS neuroimaging component*
Functional connectomics to predict tau spreading and cognitive resilience in Alzheimer’s disease

Michael Ewers

Institute for Stroke and Dementia Research (ISD)
Ludwig Maximilian University, LMU Munich
Tau pathology in Alzheimer’s disease

Tau protein stabilizes microtubules

Fibrillar tau

Braak Staging of progressive tau pathology

Pathologic Tau

Stage I-III

Stage III- IV

Stage V - VI

Aβ

PET-Tracer of fibrillar Tau

[^18F]THK5317
AD dementia, 75 yrs, MMSE 24

[^11C]THK5351
Prodromal AD, 70 yrs, MMSE 30

[^11C]PBB3
Prodromal AD, 70 yrs, MMSE 30

[^18F]AV1451
(T807, flortaucipir)
AD dementia, 74 yrs, MMSE 14

Leuzy et al. Mol. Psych. 2019
Tau spreading | functional connectivity

Resting state fMRI detected functional networks

Dorsal attention

Default Mode
Tau PET | Functional Networks

CN = controls
MCI = mild cognitive impairment

Franzmeier et al. Brain, 2019
Assessing connectivity

Resting state fMRI – functional connectivity (FC)

Brain atlas

fMRI data

Assess FC between all ROI pairs

Functional connectivity

ROI

ROI

ROI

Tau PET covariance

Tau PET

Regional tau values

Subject

ROI

ROI

ROI

ROI

Fränzle et al. Brain, 2019
Regions with high functional connectivity show covarying tau levels

Aging
Functional connectivity
Tau covariance

Alzheimer’s disease
Functional connectivity
Tau covariance

Vascular cognitive impairment
Functional connectivity
Tau covariance

\( \beta = 0.299, p < 0.001 \)
\( \beta = 0.453, p < 0.001 \)
\( \beta = 0.397, p < 0.001 \)

Franzmeier et al., Brain, 2019
Modeling future tau accumulation

Franzmeier et al. (Nature Communications, in press)
Summary

Local tau pathology
Reserve: Ability to maintain cognition relatively well at a given level of pathology.
Hub connectivity in the left lateral frontal cortex as a putative substrate of reserve

Distribution of brain hubs

Left frontal cortex (LFC) hub connectivity

- Associated with higher IQ in young subjects
### LFC connectivity in sporadic and genetically caused AD

#### Genetically caused AD from DIAN (N = 129)

<table>
<thead>
<tr>
<th></th>
<th>Mutation (n=74)</th>
<th>Controls (n=55)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>37.49 (10.05)</td>
<td>37.84 (10.31)</td>
<td>0.848</td>
</tr>
<tr>
<td><strong>Gender (f/m)</strong></td>
<td>42/32</td>
<td>34/21</td>
<td>0.563</td>
</tr>
<tr>
<td><strong>MMSE</strong></td>
<td>27.04 (5.1)</td>
<td>29.45 (1.02)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

#### Sporadic late-onset AD from DELCODE (N = 75)

<table>
<thead>
<tr>
<th></th>
<th>CN (n=25)</th>
<th>SCD (n=23)</th>
<th>MCI (n=14)</th>
<th>AD dementia (n=13)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>57.76 (5.23)</td>
<td>72.26 (4.16)</td>
<td>74.64 (5.34)</td>
<td>71.31 (6.18)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Gender (f/m)</strong></td>
<td>16/9</td>
<td>10/13</td>
<td>5/9</td>
<td>9/4</td>
<td>0.164</td>
</tr>
<tr>
<td><strong>MMSE</strong></td>
<td>29.20 (0.96)</td>
<td>29.39 (0.78)</td>
<td>27.71 (1.68)</td>
<td>23.85 (2.82)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
LFC connectivity maps

DIAN

DELCODE

Franzmeier et al., Brain 2018
Modeling the impact of global LFC connectivity on cognition

Franzmeier et al., Brain 2018
Left frontal hub connectivity modulates effect of tau on memory

82 controls & 43 MCI

Left frontal hub connectivity

Entorhinal tau PET ROI

Institute for Stroke and Dementia Research (ISD)

Neitzel et al. Neurology 2019
Model of functional brain mechanism underlying reserve

Protective factors (Education) → LFC hub connectivity → Network efficiency → Cognitive impairment

AD pathology

Neitzel et al. Neurology, 2019
Franzmeier et al. Brain, 2018
Franzmeier et al. Neurology, 2017

Network efficiency
Franzmeier et al. Alz Res Therapy, 2018

Franzmeier et al. Brain, 2018
Franzmeier et al. Neurology, 2017

Ewers et al. Neurology, 2013
Acknowledgements

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Neuroimaging Insights from the Dominantly Inherited Alzheimer’s Network (DIAN)

Beau M. Ances MD, PhD, MSc, FANA, FAAN
Daniel J Brennan MD Professor of Neurology
Departments of Neurology, Radiology, and Biomedical Engineering
Washington University in Saint Louis (WUSTL)

AABC Updates in Neuroimaging Webinar
December 9, 2019

Dr. Ances has no financial disclosures
Autosomal Dominant Alzheimer Disease (ADAD)

- A rare form of Alzheimer’s disease (AD)
  - Less than 1% of AD cases result from ADAD mutations
- Caused by an inherited gene mutation in one of three genes directly involved in amyloid beta (Aβ) production
  - Amyloid precursor protein (APP)
  - Presenilin 1 (PSEN1)
  - Presenilin 2 (PSEN2)
- 50% chance of passing the gene to a child
- Individuals with ADAD develop symptoms earlier in life
- Mutations cause predictable age of onset and allows for determination of estimated years to onset (EYO)

Auguste D., the first AD patient described by Dr. Alois Alzheimer, was later found to have an ADAD mutation in Presenilin 1 (F176L)
## Comparison of ADAD and Late Onset Alzheimer’s Disease (LOAD)

<table>
<thead>
<tr>
<th></th>
<th>ADAD</th>
<th>LOAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical presentation</td>
<td>Amnestic</td>
<td>Amnestic</td>
</tr>
<tr>
<td>Cognitive deterioration</td>
<td>Memory, frontal/executive, generalized cognitive decline</td>
<td>Memory, frontal/executive, generalized cognitive decline</td>
</tr>
<tr>
<td>Magnetic resonance imaging (MRI)</td>
<td>Hippocampal atrophy and whole brain atrophy</td>
<td>Hippocampal atrophy and whole brain atrophy</td>
</tr>
<tr>
<td>Amyloid positron emission tomography (PET)</td>
<td>Cortex <strong>plus basal ganglia</strong></td>
<td>Cortex</td>
</tr>
<tr>
<td>Flurodeoxyglucose (FDG) PET</td>
<td>Parieto-occipital hypometabolism</td>
<td>Parieto-occipital hypometabolism</td>
</tr>
<tr>
<td>Cerebrospinal fluid (CSF) Aβ 42</td>
<td>Decreased by 50%</td>
<td>Decreased by 50%</td>
</tr>
<tr>
<td>CSF tau</td>
<td>Increased by 2-fold</td>
<td>Increased by 2-fold</td>
</tr>
</tbody>
</table>

Scientific data supports drug trial for ADAD to potentially translate to LOAD.
DIAN observational study has enrolled more than 550 participants.
## DIAN Observational Cohort Demographics

**N = 562* (Target 80% Asymptomatic, 20% Symptomatic) (**Table based on 534 participants. 28 Mutations in Process)**

<table>
<thead>
<tr>
<th></th>
<th>Asymptomatic</th>
<th>Symptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>415 (73.8%)</td>
<td>145 (25.8%)</td>
</tr>
<tr>
<td>391 with confirmed</td>
<td>199 (NC)</td>
<td>11 (NC)</td>
</tr>
<tr>
<td>mutation status</td>
<td>(50.9%)</td>
<td>(7.8%)</td>
</tr>
<tr>
<td></td>
<td>192 (MC)</td>
<td>130 (MC)</td>
</tr>
<tr>
<td></td>
<td>(49.1%)</td>
<td>(92.2%)</td>
</tr>
<tr>
<td>Age, Mean (SD)</td>
<td>43.9 (12.1)</td>
<td>50.1 (11.0)</td>
</tr>
<tr>
<td></td>
<td>40.0 (10.0)</td>
<td>52.4 (9.5)</td>
</tr>
<tr>
<td>Gender (% Female)</td>
<td>118 (59.3%)</td>
<td>6 (54.5%)</td>
</tr>
<tr>
<td></td>
<td>107 (55.7%)</td>
<td>74 (56.9%)</td>
</tr>
<tr>
<td>Parental Age of Onset,</td>
<td>47.2 (6.6)</td>
<td>48.1 (5.9)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>48.5 (7.1)</td>
<td>45.6 (8.6)</td>
</tr>
<tr>
<td>Education, Mean (SD)</td>
<td>15.0 (2.8)</td>
<td>11.3 (3.8)</td>
</tr>
<tr>
<td></td>
<td>14.9 (2.8)</td>
<td>13.5 (3.3)</td>
</tr>
<tr>
<td>MMSE, Mean (SD)</td>
<td>29.2 (1.2)</td>
<td>28.2 (1.6)</td>
</tr>
<tr>
<td></td>
<td>29.0 (1.2)</td>
<td>19.4 (8.4)</td>
</tr>
<tr>
<td>ApoE4+</td>
<td>60 (30.2%)</td>
<td>3 (27.3%)</td>
</tr>
<tr>
<td>1 E4</td>
<td>56 (29.2%)</td>
<td>32 (24.6%)</td>
</tr>
<tr>
<td>2 E4</td>
<td>3 (1.5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>1 (0.5%)</td>
<td>7 (5.4%)</td>
</tr>
</tbody>
</table>

MC = Mutation Carrier; NC = Non-carrier

*Table statistics based on 534 participants with confirmed mutation data available as of 03/01/2019. Of them 323 (60.5%) are mutation carriers (of these, CDR score is missing for 1), 211 (39.5%) are mutation non-carriers (of these, CDR score is missing for 1)

- >560 participants enrolled since 2008
- Biomarker collection rate >80-90%
- More than 52% of participants are 10 years or more prior to EYO
Amyloid PET Deposition, Hypometabolism on FDG PET, and Cortical Atrophy on MRI by EYO Bateman et. al., *NEJM*, 2012

Estimated Age of Onset = -25

Estimated Years to Onset = -25.0

Benzinger et. al., 2015, *PNAS*
Comparison Between ADAD and LOAD Using Tau PET

Gordon et. al., 2018 *Brain*
Global Resting State Functional Connectivity (Rs-fc) Signature Relative to Other Biomarkers in ADAD

Smith et al., under review
Loss of Intra-Network Rs-fc in ADAD is Similar to LOAD

Thomas et al., 2014, JAMA Neurol
The Spatial Topography of ADAD is Similar But Is Accelerated When Compared to LOAD

Strain et al., under review
Stages of ADAD Based on Cross Sectional Data

- Pre-pathology
- Plaques
- Tangles

![Graph showing stages of ADAD based on cross sectional data.](image-url)

Bateman et al. NEJM 2012
Longitudinal Changes in Biomarkers in ADAD

McDade et al., 2018, Neurology
Artificial Neural Network Modeling of the Progression of Disease in ADAD Using Longitudinal Biomarkers

Luckett et al., under review
DIAN- Trials Unit (TU) Trial Platform Design

- Tests multiple drugs with diverse mechanisms of action in parallel
  - Amyloid-beta - with monoclonal antibodies and BACE inhibitors
  - Tau – anti-bodies, genetic-based therapies, small molecule aggregation inhibitors
  - Novel targets
  - Combination therapy

- Pooled placebo (including DIAN Observational Study Data)

- Adaptive in response to new findings
  - Dose adjustment to increase drug effect
  - Addition of novel biomarkers (e.g. tau PET imaging, neurofilament light chain (NfL))
  - Sensitive ADAD-specific cognitive composite endpoint
  - ADAD-specific statistical model
Through public/private support and partnership, the DIAN-TU has launched trials to provide advancement of treatments, scientific understanding and improvements in the approach to Alzheimer’s disease drug developments.

*Financial support has also been provided by anonymous sources.

**Diagnosed Early Affecting Neurons Trials Unit (DIAN-TU)**

**Alzheimer’s Association**

**DIAN-TU Pharma Consortium**

*Current Members*
- Biogen
- Eisai
- Eli Lilly & Co./Avid Radiopharmaceuticals
- Janssen
- Hoffman La-Roche/Genentech
- United Neuroscience

**National Institute on Aging**
National Institutes of Health

U01 AG042791, R01 AG046179, R01/R56 AG053267, R13 AG055232, U01 AG059798

**GHR Foundation**

**Accelerating Medicines Partnership / Foundation for the National Institutes of Health**

13 October 2019
Resources

Websites:
• DIAN & DIAN-TU: https://dian.wustl.edu/
• DIAN Expanded Registry: https://dian.wustl.edu/our-research/registry/

Contact Information:
• DIAN EXR email: dianexr@wustl.edu
• DIAN EXR Coordinator: 844-DIAN-EXR (844-342-6397)
• DIAN Observational Deputy Director 314-747-1940
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- Patrick Wright PhD
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- Jaimie Navid

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- Victor Valcour MD- UCSF
- Jaroslaw Harezlak PhD- Indiana
- David Hass PhD- Vanderbilt
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- Leah Rubin PhD- Johns Hopkins
- Joaquin Goni- Purdue

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- Marie Brouillette MD- McGill
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- John Joska MD- Capetown, South Africa
- Damien Ferguson MD- University of Dublin, Ireland
- Edwina Wright MD- Monash University, Australia
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- NIA
- NINR
- Bright Focus
- Riney Family
- Brennan Family
Thank you for your attention

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at Washington University in St. Louis

http://neuro.wustl.edu/labs/ances_b

Please contact with questions or if interested in collaborations:
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Improving Our Understanding of Alzheimer’s Disease Heterogeneity: LEADS neuroimaging component

Liana Apostolova, MD, MSc, FAAN
Barbara and Peer Baekgaard Professor of Alzheimer’s Disease Research
Clinical Core Leader, Indiana Alzheimer’s Disease Center
Department of Neurology
Indiana University School of Medicine
Funding Sources

• R56/U01 AG057195
• R01 AG057739
• R01 AG040770
• K02 AG048240
• P30 AG010133
Case 1: FORGETFUL

• 75 yo woman
• Progressive short-term memory loss - repeats herself
• Difficulty recalling names and word searching pauses
• Got lost a couple of times when driving but managed to get to her destination
• Has been forgetting to pay bills and paid one twice
• Buying duplicates
• Quieter in social situations
Case 2: “I Can’t See”

- 59 yo woman
- **Many** ophthalmologic exams and prescription changes later – no better
- Husband came back from deployment to find notes with directions all over the house
- Trouble driving – veering off
- Difficulty finding items that are right in front of her
- Confuses left and right
- Problems writing and doing math
- Memory intact
Case 3: Tongue Tied

- 76 yo man
- Significant word finding issues
- Circumlocutions
- Empty speech with heavy use of filler words ("it", "that thing", "there")
- Mispronouncing and misusing words
- Tonsils - "the things in my throat"
- Stethoscope - "you stick that in your ears and you plug it up against someone else"
- Difficulty repeating
Atrophy and Tau PET Patterns Correlate with AD Phenotype

LOAD (n=4)

EOAD (n=8)

MPPA (n=7)

PCA (n=8)

Covaried for age, p(FWE)<0.05

SCHOOL OF MEDICINE

Ossenkoppele et al., Brain 2016
Major AD Initiatives in the US

Ages of People with Alzheimer’s Dementia, 2019

- <65 years: 0.2 million (3%)
- 65-74 years: 0.9 million (16%)
- 75-84 years: 2.6 million (45%)
- 85+ years: 2.1 million (36%)

Created from data from Hebert et al.²,51
Demographics and Social Impact

• Approximately 3-5% of the 5.6 million Americans with AD (200,000-300,000)

• The second most common early onset dementia – FTD, affects ~20,000-30,000 Americans Knopman and Roberts, 2011

• Devastating consequences for patients and their families
  – Still in the workforce, not ready to retire, primary bread winners for their families
  – Many are still raising children
  – Not eligible for Medicare

• Much more aggressive disease course
Diagnostic Challenges

• Atypical presentations are very common
  • 33-50% of EOAD present with memory decline as the initial symptom compared to 75-78% of LOAD

  Mendez 2012; Jacobs1994; Koedam 2010

• Atypical variants are commonly misdiagnosed
  • Posterior cortical atrophy – vision problems, psychiatric, malingering
  • Logopenic aphasia – stroke, VaD, FTD
  • Frontal variant – FTD, TBI, psychiatric d/o
Biomarker Cascade in AD
Significance Maps (p<0.001 uncorr., cluster threshold ≥ 50 voxels)

EO-MCI vs. NC  EO-DEM vs. NC  LO-MCI vs. NC  LO-DEM vs. NC

β Coefficient Maps

β Coefficients

[Data and analysis related to MRI images and significance maps]
FDG PET

Significance Maps (p<0.001 uncorr., cluster threshold ≥ 50 voxels)

EO-MCI vs. NC
EO-DEM vs. NC
LO-MCI vs. NC
LO-DEM vs. NC

β Coefficient Maps

β Coefficients

SCHOOL OF MEDICINE

Stage et al, submitted
Tau PET - AD
Significance Maps (p_{cluster-level FWE}<0.05)

EO-MCI vs. NC

EO-DEM vs. NC

LO-MCI vs. NC

LO-DEM vs. NC

β Coefficient Maps

β Coefficients

-0.5 0.0 0.2 0.5
### 2018 NIA-AA Research Framework

| A-T-(N)- | Normal Alzheimer’s biomarkers |
| A+T-(N)- | Alzheimer’s pathologic change |
| A+T+(N)- | Alzheimer’s disease |
| A+T+(N)+ | Alzheimer’s disease |
| A+T-(N)+ | Alzheimer’s and suspected non-Alzheimer’s pathologic change |
| A-T+(N)- | Non-Alzheimer’s pathologic change |
| A-T-(N)+ | Non-Alzheimer’s pathologic change |
| A-T+(N)+ | Non-Alzheimer’s pathologic change |

**A** = Amyloid; **T** = Tau; **N** = Neurodegeneration

Recruitment

• 20 US academic institutions
• 15 sites across the US
• Recruitment goals:
  – 400 subjects meeting NIA-AA criteria for MCI due to AD or AD dementia ages 40-64 with global CDR ≤ 1
    • Subjects meeting criteria for lvPPA, PCA or frontal variant AD will be allowed
    • Subjects with $APP$, $PSEN1$, $PSEN2$ mutation will be excluded
  – 100 cognitively normal subjects ages 40-64
  – NEW: Will also follow amyloid-negative group - N=200
# Demographics

<table>
<thead>
<tr>
<th></th>
<th>CN</th>
<th>EOAD</th>
<th>EAnonAD</th>
<th>EOADvsCN</th>
<th>EOnonADvsCN</th>
<th>EOAD vs. EOnonAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>47</td>
<td>77</td>
<td>23</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Age</td>
<td>54.4 (6.0)</td>
<td>58.3 (4.0)</td>
<td>58.0 (6.0)</td>
<td>0.0016</td>
<td>0.022</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>16/31</td>
<td>32/45</td>
<td>17/6</td>
<td>NS</td>
<td>0.0039</td>
<td>0.013</td>
</tr>
<tr>
<td>Education, yrs.</td>
<td>16.9 (2.4)</td>
<td>15.6 (2.6)</td>
<td>15.6 (2.5)</td>
<td>0.048</td>
<td>0.043</td>
<td>NS</td>
</tr>
<tr>
<td>MMSE</td>
<td>29.3 (0.8)</td>
<td>21.9 (4.9)</td>
<td>26.0 (2.5)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Amyloid PET – Mean SUVR

EOAD

EOnonAD

CN

$^{18}$F-Florbetaben SUVR

0.5  

2.5
MRI Results - Hippocampus

% of subjects 1.5 SD below control mean: EOAD 74%  EOnonAD 48%
MRI Results – Cortical Thickness

% of subjects 1.5 SD below control mean:

AD signature: EOAD 78%  EOnonAD 43%
Precuneus: EOAD 87%  EOnonAD 48%
MRI Results - Cortical Thickness

EOAD vs CN

EOnonAD vs CN

Cohen’s D

-1.5 - .5 .5 1.5

L L R R

SCHOOL OF MEDICINE
Tau PET Results
Genetic Heterogeneity in EOAD

- Common misconception: All EOAD cases are autosomal dominant.

- Greater heritability in EOAD compared to LOAD suggests an enrichment for yet unknown genetic risk factors:
  - 92%-100% heritability in EOAD vs. 70%-80% LOAD
  - fewer EOAD compared to LOAD carry ApoE4
Towards Precision Medicine

Adapted from Yan et al., Briefings in Bioinformatics, 2018
LEADS Study Investigators