Current research in action: Neuroimaging and Biomarkers in Alzheimer disease

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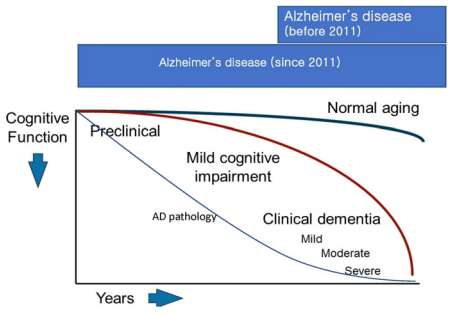
Biomarkers in Alzheimer disease

- Fluid biomarker
  - CSF biomarker
  - Blood biomarker
- Neuroimaging biomarker
  - Structural image biomarker
  - Functional image biomarker
  - Molecular image biomarker
  - Electrophysiological biomarker

Diagnosis of Alzheimer disease



Biomarker studies in Alzheimer disease

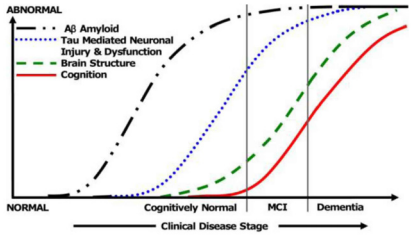
- Have converged to preclinical stage of AD.
- Clinical trials targeted preclinical stage population for AD 2nd prevention.
  - Being used for subject enrollment,
  - Proof of therapeutic target
  - Surrogates for the effects on disease pathology.
- Elucidates the trajectories of biomarker changes during the natural course of the AD.

Biomarker studies in Alzheimer disease

- **Autosomal Dominant AD** vs sporadic AD
  - Aβ accumulation mechanism
    - Amyloid plaque and NF tangle, neuronal loss ..
  - Earlier and more severe pathology
  - non-memory, non-cognitive neurological symptoms
- Asymptomatic period study 장점
  - Future dementia will develop
  - Relatively predictable age at symptom onset
  - Age related co-morbidity 배제

Biomarker studies in Alzheimer disease

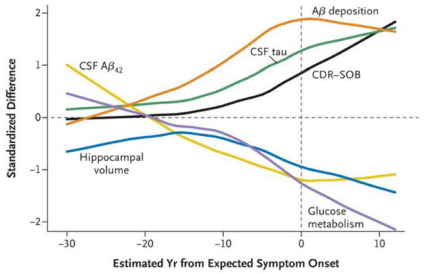
Proposed Alzheimer's disease pathological cascade based on biomarkers



Biomarker studies in Alzheimer disease

Clinical and Biomarker Changes in DIAN

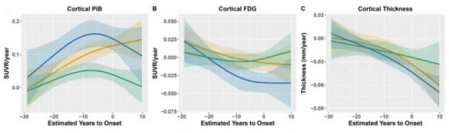
-cross-sectional analysis



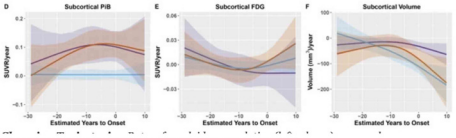
N Engl J Med. 2012 Aug 30;367(9):795-804

Biomarker studies in Alzheimer disease

Changing Trajectories in DIAN



inferior temporal (orange), precuneus (blue), and insula (green)



caudate (purple), putamen (red), and hippocampus (turquoise)

Brian Gordon, AAIC 2017

Biomarker studies in Alzheimer disease

- Asymptomatic phase
  - CSF and plasma Aβ 1-42 ↑, very early in the pre-symptomatic phase MC of ADAD.
  - CSF Aβ 1-42 ↓, sequestered in β-amyloid plaques.
  - CSF tau and p-tau 181 ↑ , tangle formation with neuronal degeneration
- Symptomatic phase
  - Slower rate than earlier stage → decrease of tau and p-tau 181
- Consistent with cross-sectional studies in LOAD
  - Early increase in these markers followed by later decrease
  - Size of neuronal populations undergoing acute injury

Biomarker studies in Alzheimer disease

Are CSF and PET measuring equivalent?

- PET signal, accumulation of fibrils in the brain. CSF markers of Aβ and tau, balance btw production and clearance of soluble form (Susan Landau)
- PET and CSF markers follows distinct trajectories (Toledo et al, 2015)
  - CSF Aβ ↓, early preclinical stage and stays low
  - Amyloid PET signal rises steadily and falls, inverted U curve.
- CSF reflect a pathophysiological state, PET scan stages the disease (Clifford Jack)
  - PET scan, better in measuring progression and trial outcomes.

Biomarker studies in Alzheimer disease

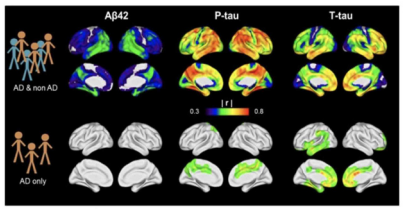
Are CSF and PET measuring equivalent?

- tau PET signal correlated positively with CSF tau and negatively with CSF Aβ. → work for diagnosis
- CSF p-tau, process specific to AD, t-tau, general neurodegeneration
- Strong correlation btw **CSF p-tau** and **tau PET** (Renauld La Joie AAIC 2017)
- **CSF p-tau** and **tau PET** as marker of tau pathology, **CSF t-tau** is considered a neurodegeneration (Chhatwal et al. 2016)

Biomarker studies in Alzheimer disease

Tau PET will provide a more useful progression marker

- Tau PET signal **correlated poorly** with CSF Aβ or CSF tau **in the AD**
- CSF and PET measures are not interchangeable for scoring severity of AD



Renaud La Joie AAIC 2017

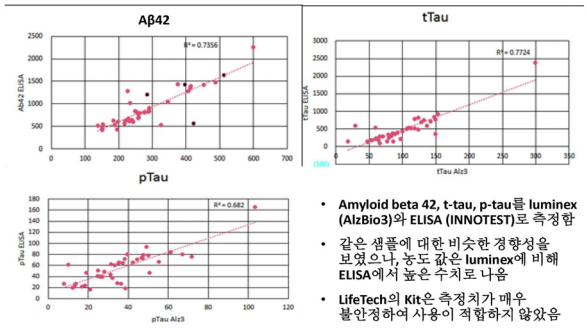
Biomarker studies in Alzheimer disease

Tau PET will provide a more useful progression marker

- Tau PET signal correlated with **symptom severity**, **brain atrophy** and **cognitive decline** better than CSF tau did. (AAIC 2017, 2016)
- CSF tau does not track progression through the symptomatic stage of AD. (La Joie, AAIC 2017)

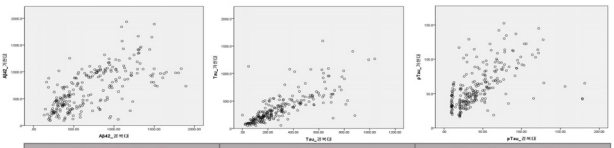
→ Tau PET will provide a more useful progression marker.

Luminex Vs. ELISA



- **Amyloid beta 42, t-tau, p-tau**를 **luminex (AlzBio3)**와 **ELISA (INNOTEST)**로 측정함
- 같은 샘플에 대한 비슷한 경향성을 보였으나, 농도 값은 **luminex**에 비해 **ELISA**에서 높은 수치로 나옴
- **LifeTech**의 **Kit**은 측정치가 매우 불안정하여 사용이 적합하지 않았음

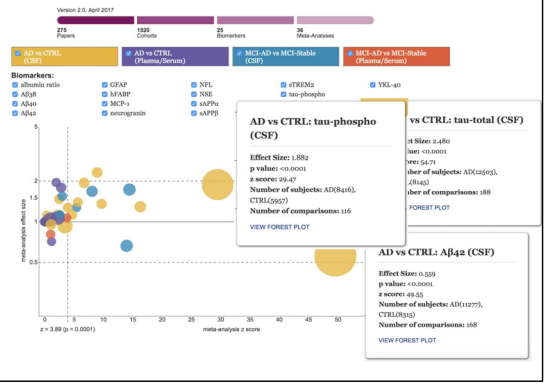
Inter-center 신뢰도



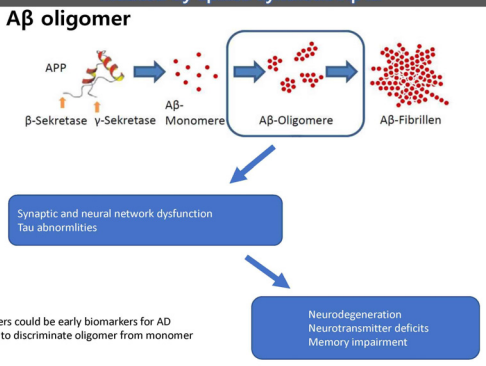
Amyloid-ß 1-42	Total Tau	Phosphorylated Tau
ICC = 0.799	ICC = 0.860	ICC = 0.732
P<0.001	P<0.001	P<0.001

http://www.alzforum.org/alzbiomarker

Fluid biomarkers



Dynamic changes of oligomeric amyloid β levels in plasma induced by spiked synthetic Aβ42

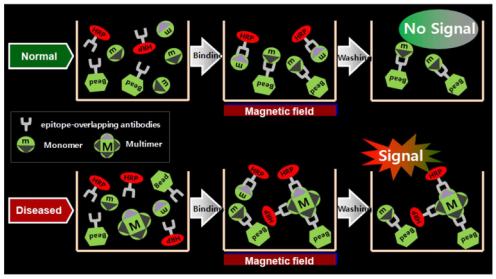


- Aß oligomers could be early biomarkers for AD
- Need tech to discriminate oligomer from monomer

Dynamic changes of oligomeric amyloid β levels in plasma induced by spiked synthetic Aβ42

Multimer Detection System

Competition assay using capturing antibodies (conjugated with magnetic-beads) and epitope-overlapping detection antibodies (conjugated with HRP) for the detection of only oligomers from monomers in protein-misfolding diseases.



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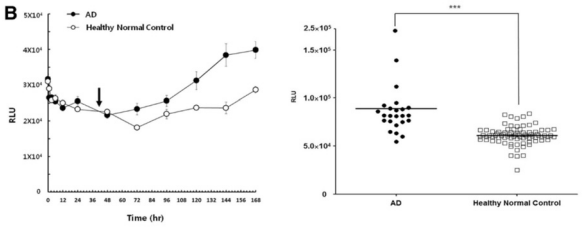
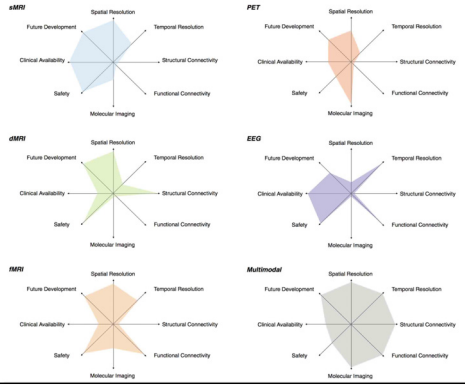


An et al. Alzheimer's Research & Therapy (2017) 9:86

Brain Inform. 2015 Sep; 2(3): 167–180.

Neuroimaging Biomarkers



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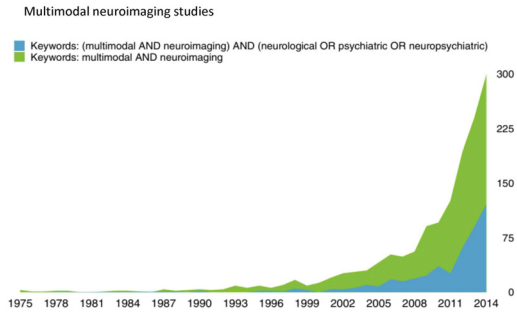
Neuroimaging Biomarkers



Neuroimaging Biomarkers

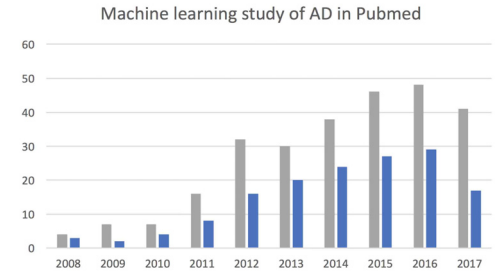
- Multimodal neuroimaging studies
  - Structural – structural combination
    - sMRI-dMRI
  - Functional – functional combination
    - Brain activation/metabolic pattern
  - Structural – functional combination
    - Structure and function associations in neurodegenerative dis

Neuroimaging Biomarkers

- Future direction of multimodal neuroimaging studies
  - Have been increasingly used in detection, diagnosis, prognosis and treatment planning
- Improving neuroimaging capabilities
  - Standardization
  - Clinical guidline
- Enhancing neuroimaging computing models and methods
  - Longitudinal data → understanding pathology and predictiong course
  - Subject centered imaging study
- Converging neurotechnologies
  - Imaging and non-imaging studies
  - Imaging genetics

Neuroimaging Biomarkers

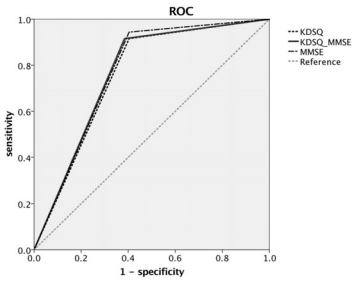
Machine learning for AD



Machine learning for dementia screening

- CREDOS data
  - Obtained the original dataset for 10,189 subjects
  - The training and test data set were randomly allocated with 9885 and 300 subjects.
- 24 variables
  - sex; age at the time of a visit; education duration; diabetes mellitus; hypertension; hypercholesterolemia; stroke history; 15 item score of the KDSQ; the MMSE score; and the outcome variable
- We trained a machine learning algorithm using TensorFlow (https://www.tensorflow.org/) based on the training data set and then calculated its accuracy with the test data set. The cost was calculated by conducting a logistic regression.

The algorithm in predicting cognitive impairment



	accuracy	sensitivity	specificity
KDSQ	84.3%	91.50%	59.60%
MMSE	88.3%	94.35%	59.62%
KDSQ+MMSE	86.3%	91.50%	61.50%

Machine learning for dementia screening

- Subjects
  - Training dataset 289, Test dataset 55
- KDSQ + image data
  - Image data
    - 3D T1 image
    - Freesurfer
    - Bilateral hippocampal vol, WMHI volume
- TensorFlow (https://www.tensorflow.org/)
- The cost was calculated by conducting a logistic regression.
- Accuracy: 92.7%

Summary

- Biomarker studies have converged to preclinical stage of AD
- Biomarkers change in the different patterns, and vary by brain region and disease state.
- PET and CSF markers follows distinct trajectories
- Tau PET will provide a more useful progression marker.
- CSF biomarker standardization
- Multi-modal Neuroimaging studies
- Machine learning